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WOUNDS OF THE HEART

COL. DANIEL C. ELKIN, M.C., A.U.S.

FROM THE WHITEHEAD DEPARTMENT OF SURGERY, EMORY UNIVERSITY, ATLANTA, GA.

IN NOVEMBER, 1940, I made a report concerning 38 patients who had been operated upon for wounds of the heart or intrapericardial portions of great vessels.[1] All of these patients were operated upon in the Emory University Division of Grady Hospital, Atlanta. Since that time 23 patients have been operated upon in the same clinic for similar conditions, and these latter cases are here reported in abstract, with further observations upon this condition, particularly as regards its treatment.

With the exception of Case 1 the patients in this latter series were operated upon by members of the Resident Staff, and to them should go full credit for the continued interest in this field of traumatic surgery. Of these 23 patients there were five deaths, a mortality of 22 per cent, whereas, in the previously reported 38 patients 16 died, a mortality of 42 per cent—a combined mortality in the 61 patients of 34 per cent. It is believed that this reduction in death rate was due to several factors. The resident surgeons who performed these operations have gone through a period of graduated preparatory training during which time they are allowed to assist in and perform procedures of this type on their own responsibility and, as a result, become more skillful in the performance of such operations. Moreover, they are constantly on the alert to make a proper diagnosis and in proceeding with treatment with the least possible delay.

In the first series seven deaths were recorded as due to infection; pericarditis, pneumonia, and bacteriemia. In the latter series there were no deaths from infection, and those patients who did not recover either died on the operating table, or shortly thereafter, presumably from hemorrhage or from the effects of tamponade. The reduction in mortality from infection was not due to the use of sulfa drugs since in the second series it was only used in one case (Case 1) for the treatment of postoperative pneumonia. In no instance has it been placed in the wound. I believe that the reduction in infections is, in the main, due to a more meticulous technic and in careful preoperative preparation. In no instance of the latter series has careful preparation and operative technic been sacrificed for speed and haste.

Another factor which may be of considerable importance has been the giving of intravenous fluid prior to operation. I was formerly of the opinion, which was largely based upon the work of Beck,[2] that *in the presence of*

tamponade, the giving of blood or any other fluid intravenously was of no value since the tamponade would prevent its reaching the heart. The experimental work of Cooper, Stead, and Warren[3] presents evidence that the rapid intravenous infusion, with subsequent increase in blood volume, enables a dog to withstand a considerably higher intrapericardial pressure. Based upon this conclusion, intravenous infusions were given to the last eight patients, and in each there was a clinical improvement preoperatively.

All the patients in this series, as well as those previously reported, were operated upon since in each there was definite evidence of cardiac tamponade. This diagnosis was based upon the lowered arterial pressure and increased venous pressure; and the presence of a quiet heart as noted on fluoroscopic examination. This latter diagnostic point was first described by Bigger,[4] and has since been emphasized by others. Of all signs leading to a diagnosis of tamponade this is the most important and is the one least likely to lead to a mistaken diagnosis.

Venous pressure readings are not only of value in the diagnosis of tamponade but are of considerable prognostic importance. If the venous pressure is high, that, in itself, is evidence that the heart is carrying on its functions and that the cardiac output is at least sufficient to produce such pressure. On the other hand, a low or lowered venous pressure in the presence of tamponade is evidence of a failing heart and of a greatly reduced cardiac output. In this connection, it is interesting to note that Case 9, with a venous pressure of 120 mm. of water, died two hours after operation; that Case 16, with venous pressure of 150 mm. of water, died on the table, and that Case 21, with venous pressure of 210 mm. of water, died on the table.

It will be noted that in all patients there was a definite lowering of the arterial pressure, and in 17 of the 23 blood pressure readings could not be recorded. In those patients who recovered there was an immediate rise in arterial pressure following the release of the tamponade.

Some type of general anesthesia in which positive pressure can be used for inflation of the lung is preferable to local anesthesia. The difficulties of heart suture require that the patient be quiet, and these patients are usually excited or may become so with the release of the tamponade and, unless completely anesthetized, their movements may interfere with the operation at the most inopportune time.

As previously pointed out, the approach to the heart is made on the left side of the sternum with the incision placed about one intercostal space below the external wound. In most instances a transverse incision extending from about two centimeters outside the nipple line and carried well across the sternum has been used. By this approach one or two ribs can be removed, and, if necessary, the adjacent costal cartilages cut and a portion of the sternum removed. The pectoralis major muscle is separated in the direction of its fibers and can be retracted from the surface of the three ribs. Every care should be taken to prevent opening the pleura since such a complication adds materially to the shock which the patient has already undergone. The

TABLE I

SUMMARY OF 23 CASES OF CARDIAC WOUNDS

No.	Operator*	Sex	Age	Instrument	Duration from Injury to Operation	H_2O Venous Pressure	Arterial Pressure on Admission	Arterial Pressure after Operation	Tamponade	Location	Complications	Amount of Blood Given	Result
1.	D.C.E.	F.	27	Ice pick	80 mins.	250 mm.	0/0	110/70	+	R. auricle	Pneumonia	750 cc.	Recovery
2.	C.S.W.	M.	33	Knife	60 mins.	200 mm.	60/40	120/80	+	R. ventricle	L. hemothorax	300 cc.	Recovery
3.	C.S.W.	M.	27	Knife	60 mins.	220 mm.	80/55	130/70	+	Pul. conus	L. hemothorax	500 cc.	Recovery
4.	C.S.W.	M.	28	Knife	60 mins.	270 mm.	0/0	110/80	+	R. ventricle	L. hemothorax	1000 cc.	Recovery
5.	W.C.W.	M.	25	Knife	60 mins.	230 mm.	50/35	120/70	+	Pul. conus	L. hemothorax	600 cc.	Recovery
6.	R.F.M.	F.	31	Knife	75 mins.	190 mm.	0/0	110/80	+	L. ventricle	None	600 cc.	Recovery
7.	R.F.M.	M.	23	Ice pick	90 mins.	210 mm.	0/0	100/50	+	L. ventricle	None	600 cc.	Recovery
8.	F.W.C.	M.	28	Knife	40 mins.	190 mm.	0/0	100/60	+	R. ventricle (ant. and post.)	R. hemothorax Pneumonia.	1000 cc.	Recovery
9.	F.W.C.	M.	40	Knife	90 mins.	120 mm.	0/0	110/70	+	Pul. artery	Died	1000 cc.	Died—2 hrs.
10.	W.C.W.	F.	19	Knife	90 mins.	200 mm.	0/0	0/0	+	R. ventricle	Died	800 cc.	Died—2 hrs.
11.	W.C.W.	M.	24	Knife	90 mins.	160 mm.	0/0	110/70	+	R. ventricle	R. hemothorax	1000 cc.	Recovery
12.	W.C.W.	M.	18	Knife	80 mins.	110 mm.	50/0	100/80	+	R. ventricle	L. hemothorax	1000 cc.	Recovery
13.	F.W.C.	M.	41	Knife	60 mins.	250 mm.	0/0	160/80	+	L. ventricle	L. hemothorax	1000 cc.	Recovery
14.	C.M.H.	M.	26	Knife	45 mins.	190 mm.	0/0	0/0	+	Pul. artery	Died	500 cc.	Died—10 mins.
15.	W.C.W.	M.	22	Knife	120 mins.	180 mm.	0/0	160/60	+	R. ventricle	None	600 cc.	Recovery
16.	W.C.W.	M.	27	Knife	90 mins.	150 mm.	0/0	0/0	+	L. auricle	Died	1000 cc.	Died on table
17.	C.M.H.	M.	44	Knife	60 mins.	190 mm.	80/50	110/70	+	Aorta	None	1500 cc.	Recovery
18.	W.H.P.	M.	43	Knife	60 mins.	210 mm.	0/0	120/70	+	R. auricle	L. hemothorax	1500 cc.	Recovery
19.	C.M.H.	M.	36	Knife	60 mins.	200 mm.	70/40	130/70	+	R. ventricle	Pericardial effusion	1500 cc.	Recovery
20.	W.H.P.	M.	29	Knife	60 mins.	190 mm.	0/0	120/70	+	Pul. artery (2 openings)	L. hemothorax	2000 cc.	Recovery
21.	W.H.P.	F.	33	Knife	120 mins.	120 mm.	0/0	0/0	+	Undetermined	Died	1000 cc.	Died on table
22.	W.H.P.	M.	52	Ice pick	120 mins.	210 mm.	0/0	120/60	+	Pul. artery	L. hemothorax	1500 cc.	Recovery
23.	W.H.P.	M.	50	Knife	90 mins.	220 mm.	0/0	110/70	+	Pul. conus	Pneumonia	1000 cc.	Recovery

* The operating surgeons referred to by initial in the summary of these cases were Doctors Charles S. Ward, W. Cleve Ward, Robert F. Mabon, F. W. Cooper, Chas. M. Harris, and Wm. H. Proctor.

internal mammary vessels must be carefully isolated and ligated. They may not bleed before the tamponade is released, but later hemorrhage from them may be fatal unless proper ligation has been performed. The pleura on the left is displaced from the pericardium by gauze dissection and held out of the wound by a wet pack. As a rule, the pericardium will be tense, and its pulsations weak or imperceptible. If the wound in the pericardium is seen it should be enlarged or, if not readily found, it is opened between stay-sutures. Occasionally the heart wound can be located before the blood and clots are removed and before the heart starts beating actively, and under such conditions it can be readily sutured. More often the heart wound is not disclosed until blood and clots are removed by suction. When the intrapericardial pressure is relieved the bleeding becomes marked and contractions of the heart increase in force. When the wound is located, and it is most often found in the right ventricle, its closure is facilitated by placing the left index finger over it. In this way the bleeding will be impeded sufficiently to allow the passage of a suture directly under the finger. This is left untied for the moment and is held in the left hand for traction hemostasis while other sutures are placed and tied. Should the wound be behind the sternum or on the posterior surface of the heart a stay-suture passed through the apex, as advocated by Beck,[5] is of great value. By this means the wound may be rotated into a favorable position for suture. It is to be noted that there were two instances of double wounds; one of the pulmonary artery with recovery, and one in the anterior and posterior surface of the right ventricle, which recovered. In this second case the use of the apex stay-suture was of particular value in rotating the heart into a position where the posterior wound could be successfully sutured. Wounds of the coronary vessels may require ligature but are not necessarily fatal. Beck[2] has recently devised an ingenious method of suturing wounds in the vicinity of the coronary vessels without injuring them. The pericardium should be closed loosely to allow the escape of pericardial fluid, but the chest wall should be sutured with careful approximation of the anatomic layers. Details concerning the suture of wounds of the auricles and great vessels have been previously described.[1]

The opinion was expressed by me in a previous paper[1] that operation should be carried out as soon as the diagnosis of a heart wound is established. In view of the reports from other clinics on this subject this opinion should probably be modified to include some form of conservative treatment if conditions are not urgent and operation does not seem to be immediately demanded. Bigger,[6] Strieder,[7] and Blalock[8] have emphasized the value of aspiration of the pericardium as a preliminary to operation, and in some instances it has been found that aspiration alone is the only operative procedure necessary, since some wounds, particularly those which do not penetrate the cavities of the heart, have sealed, and aspiration of the blood relieving the tamponade is sufficient to bring about a cure. Blalock[8] advocates that in cases of tamponade where there is no bleeding into the chest or to the

outside, that the pericardium be aspirated, but that "all facilities should be available for immediate operation if it becomes necessary." He further states that "if blood reaccumulates rapidly following aspiration, it is agreed that exposure and suture of the heart wound is indicated." He also makes a statement that "if one has good reason to believe that an auricle rather than a ventricle has been injured, one may more safely defer operation." I do not believe there is any method whereby it may be determined whether an auricle, a ventricle, or the intrapericardial portion of a great vessel is the point of injury. The direction of the knife-thrust or a bullet wound is notoriously misleading, and the position of the cardiac wound cannot be determined by the wound of entrance, and the symptoms of tamponade are the same no matter what the source of the bleeding. It would seem then that the only modification of the advocacy of immediate suture would be continued improvement following aspiration without recurrence of the signs of cardiac compression.

CONCLUSIONS

Twenty-three patients operated upon for wounds of the heart are presented in abstract. These are in addition to 38 cases of similar nature previously reported from the Department of Surgery, Emory University, Grady Hospital, Atlanta. The mortality rate in the latter series was 22 per cent as compared with 42 per cent in the first series.

Conjectured reasons for this lower mortality rate are presented.

It is believed that the giving of intravenous infusions prior to operation has a beneficial effect by increasing blood volume and, hence, cardiac output.

While immediate operation was undertaken in all patients of this series, and carried out as soon as diagnosis was made, it appears evident from the reported cases of other clinics that aspiration of the pericardium, both as a temporary and definitive method of treating cardiac tamponade may be properly employed. Operation should not be delayed if there is evidence of bleeding into the pleural cavity or through the external opening.

REFERENCES

[1] Elkin, D. C.: The Diagnosis and Treatment of Cardiac Trauma. ANNALS OF SURGERY, **114**, 169, August, 1941.

[2] Beck, C. S.: Further Observations on Stab Wounds of the Heart. ANNALS OF SURGERY, **115**, 698, April, 1942.

[3] Cooper, Fred W., Jr., Stead, Eugene A., Jr., and Warren, James V.: The Beneficial Effect of Intravenous Infusions in Acute Pericardial Tamponade. ANNALS OF SURGERY, **120**, 822, December, 1944.

[4] Bigger, I. A.: Wounds of the Heart and Pericardium. South. Med. Jour., **25**, 785, 1932.

[5] Beck, C. S.: Wounds of the Heart. Arch. of Surg., **13**, 205, 1926.

[6] Bigger, I. A.: Heart Wounds: Report of Seventeen Patients Operated upon in Medical College of Virginia Hospitals: Discussion of Treatment and Diagnosis. Jour. Thor. Surg., **8**, 239, 1939.

[7] Strieder, J. W.: Stab Wound of the Heart. Jour. Thor. Surg., **8**, 576, 1939.

[8] Blalock, Alfred, and Ravitch, Mark M.: A Consideration of the Nonoperative Treatment of Cardiac Tamponade Resulting from Wounds of the Heart. Surg., **14**, 157, August, 1943.

THE BENEFICIAL EFFECT OF INTRAVENOUS INFUSIONS IN ACUTE PERICARDIAL TAMPONADE*

FRED W. COOPER, JR., M.D., EUGENE A. STEAD, JR., M.D.,
AND
JAMES V. WARREN, M.D.

ATLANTA, GA.

FROM THE SURGICAL AND MEDICAL SERVICES OF THE GRADY HOSPITAL, AND THE DEPARTMENTS OF SURGERY AND MEDICINE, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA, GEORGIA

ALTHOUGH STAB WOUNDS of the heart with pericardial tamponade are not common, they do constitute a unique and serious problem in emergency therapy. These patients usually arrive at the hospital in profound shock, with coma, cold, clammy extremities, unobtainable arterial pressure, and distended veins. Knowledge of the circulatory dynamics is not only of considerable theoretic interest, but of practical importance in therapy as well. It is obvious that the circulation can be maintained only as long as the venous pressure exceeds the elevated intrapericardial pressure. It was felt that a consideration of the factors leading to elevation of the venous pressure might lead to a more rational basis for therapy.

The elevated venous pressure in pericardial tamponade is usually said to be produced by damming up of blood behind the obstruction to the venous inflow to the heart, much as a dam causes a stream to fill up and form a lake. Such an analogy is applicable to the increase in venous pressure which is produced in an extremity by blocking the venous outflow with a tourniquet. The retained blood fills and distends the veins of the part until the pressure within them can overcome the block. At this point the veins of the extremity contain more blood than before, this blood being obtained by compensatory vasoconstriction in other parts of the body. By this method the venous pressure in a part can be elevated practically to the level of the systolic arterial pressure. It must be remembered that the lake is formed not with the water that is continually being added to the stream from above. Thus, the analogy of the dammed stream in its entirety is not applicable in pericardial tamponade, because the circulation is a closed system in which the venous inflow to the heart is dependent upon the cardiac output. The amount of venous distention which can be caused by damming up the venous inflow to the heart is limited by the fact that a decrease in cardiac output rapidly diminishes the stream of blood entering the venous system. The venous pressure must be raised in some manner by the use of blood already in the vascular bed and not by blood being constantly fed into it from fresh sources. Blood in small amount is obtained by vasoconstriction forcing blood in peripheral vascular beds into the larger veins. With the fall in arterial pressure less blood is contained in the arterial tree, and this blood also becomes avail-

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Emory University School of Medicine.

able to fill and distend the venous system. Thus, the rise in venous pressure is produced by a combination of vasoconstriction and redistribution of blood in the vascular bed. It must be remembered that most patients with stab wounds of the heart have lost blood externally, so that the vasoconstrictor mechanisms have already been called into play to compensate for the decrease in blood volume. Under these conditions the body is at a disadvantage in attempting to raise the venous pressure to overcome the tamponade.

Another method by which the venous pressure may be elevated is an increase in blood volume. This is an important mechanism in the elevation of the venous pressure in chronic congestive heart failure, but does not operate in acute pericardial tamponade because the onset is almost instantaneous. The capillary pressure throughout the body is elevated, so that rapid passage of fluid into the blood stream does not occur. Since survival in pericardial tamponade is dependent upon elevation of the venous pressure, it appeared that the use of intravenous fluids to raise the venous pressure by increasing the blood volume might be beneficial. The following experiments were undertaken to test such an hypothesis.

Methods.—Medium-sized dogs were used, two of which were subject to splenectomy two weeks prior to the experimental procedure. Under sodium pentobarbital anesthesia, and with positive pressure artificial respiration, the left pleural space was opened and the pericardium exposed. A flanged metal tube, similar to that used by Katz and Gauchet,[1] was inserted into the pericardium and screwed down to form a water-tight junction. A small rubber tube attached to the metal one traversed the dorsal portion of the left chest. The wound was closed tightly about the rubber tube and the air remaining in the pleural space was aspirated.

Several hours later the experiments were conducted. At this time the animals breathed naturally, without difficulty, and were alert and active. The rubber tube was connected with a reservoir of physiologic saline solution so that the intrapericardial pressure could be varied at will. A No. 8 ureteral catheter was inserted in the superior vena cava and the central venous pressure measured directly in centimeters of water. The mean arterial pressure was obtained in some experiments by direct femoral puncture. At the conclusion of the experiment, the operative site was examined to check the position and function of the tube in the pericardium.

Results.—Experiments were carried out upon five dogs. In all, rapid elevation of the pericardial pressure produced similar results. As the saline reservoir was raised, the venous pressure rose concomitantly, remaining slightly above the intrapericardial pressure. The arterial pulse became paradoxical in quality and finally was imperceptible. As the pressure was increased the respirations became irregular and gasping, then ceased, usually with the heart still beating. If the pressure was released at this time, the respirations would usually resume, although at times artificial respiration would be necessary for a few minutes. The response of the splenectomized dogs appeared no different from those with the spleen intact.

The pressure required to produce such symptoms was quite constant for a given dog, but varied considerably from animal to animal. It ranged from 12 to 22 cm. of H_2O pressure. After determination of the pressure required to produce such severe symptoms, a rapid intravenous infusion of physiologic saline solution was given to temporarily increase the blood volume. That it did so was demonstrated by a fall in hematocrit reading and plasma protein concentration. Several minutes after infusion was started the ability of the dog to withstand increased pericardial pressure was retested. In three such experiments the dog withstood 92, 95, and 146 per cent greater pressure than previously. In two instances after the blood volume had returned to normal, the ability to withstand increased pericardial pressure had diminished and the entire procedure was repeated, with similar results.

In human cases of pericardial tamponade the situation is slightly different, in that the tamponade is already present when therapy is started and the rent in the pericardial sac is usually closed. Therefore, two experiments were conducted with a closed system. Severe tamponade was produced and the lumen of the rubber tube leading from the pericardium was then occluded. In both of these dogs there was distinct improvement with the administration of approximately 300 cc. of saline solution. In the one instance the mean arterial pressure rose from 40 Mm. Hg. to 78 Mm. Hg. The intrapericardial pressure and venous pressure as measured after improvement rose less than two centimeters of water.

COMMENT.—The pressure in the pericardium necessary to produce circulatory failure in our dogs was similar to that previously reported.[1] The effects of saline infusion are similar to those reported by Beck,[2] except that he was unable to obtain improvement when the tube leading to the pericardium was clamped off. From a theoretic standpoint, it appears that improvement in the circulation under these circumstances would depend upon the ability of the pericardium to stretch and allow an adequate cardiac filling with the increased venous pressure. In our dogs such stretching appeared to occur, and the increased pericardial pressure was more than compensated by the increased venous pressure.

The physiologic alterations in acute pericardial tamponade are not similar to those in chronic constrictive pericarditis. In the latter condition cardiac filling is prevented by dense fibrous tissue no matter how high the venous pressure becomes. In acute pericardial tamponade filling can occur if the venous pressure sufficiently exceeds the intrapericardial pressure and if the pericardium is able to stretch.

Opinions differ as to whether the intravenous administration of physiologic saline solution is beneficial in patients with acute pericardial tamponade resulting from a stab wound of the heart or great vessels. In the patients who survive until they reach the hospital the myocardial, and probably the pericardial, rents are at least temporarily closed. Bigger[3] states that intravenous infusions are useful. Elkin,[4] and Griswold and Maguire[5] believe that they are of little benefit. Stimulated by the favorable results in experi-

ments on the dogs, saline infusions have been administered to the last three patients admitted to Grady Hospital with traumatic pericardial tamponade. In each case the arterial pressure rose and the patients became more rational. At operation, the wounds in the heart and pericardium were found to have remained sealed, in spite of the rise in arterial pressure.

Blalock and Ravitch[6] have recently emphasized that the tamponade can frequently be relieved by aspirating the pericardium. They stressed the fact that in many instances the bleeding does not recur and that operation is not necessary. The results reported here suggest that the circulatory failure in acute pericardial tamponade is helped by the use of intravenous infusions. This form of therapy serves as a useful adjunct to the treatment either by aspiration or by operation. It is possible that, in certain selected patients, raising the venous pressure by increasing the blood volume will restore the circulation to an adequate level without either aspiration or operation.

SUMMARY AND CONCLUSION

1. Acute pericardial tamponade was produced in dogs. The pressure required to produce severe symptoms varied from 12 to 22 cm. of water.

2. A rapid intravenous infusion, with subsequent increase in blood volume, enabled the dogs to withstand 92 to 146 per cent greater pressure.

3. In two dogs severe tamponade was produced, and intravenous saline solution caused striking improvement, even though the pericardium was closed and no fluid escaped.

4. Preliminary observations upon patients with acute pericardial tamponade from stab wounds of the heart indicate that the preoperative administration of intravenous fluids is beneficial.

REFERENCES

[1] Katz, L. N., and Gauchat, H. W.: Observations on Pulsus Paradoxus (with Special Reference to Pericardial Effusions). II Experimental. Arch. Int. Med., **33**, 371, 1924.

[2] Beck, C. S.: Further Observations on Stab Wounds of the Heart. ANNALS OF SURGERY, **115**, 698, 1942.

[3] Bigger, I. A.: Heart Wounds: Report of 17 Patients Operated upon in Medical College of Virginia Hospitals: Discussion of Treatment and Prognosis. Jour. Thor. Surg., **8**, 239, 1939.

[4] Elkin, D. C.: The Diagnosis and Treatment of Cardiac Trauma. ANNALS OF SURGERY, **114**, 169, 1941.

[5] Griswold, R. A., and Maguire, C. H.: Penetrating Wound of the Heart and Pericardium. Surg., Gynec. & Obst., **74**, 406, 1942.

[6] Blalock, A., and Ravitch, M. M.: A Consideration of the Nonoperative Treatment of Cardiac Tamponade Resulting from Wounds of the Heart. Surgery, **14**, 157, 1943.

SYNOVIAL SARCOMA

CUSHMAN D. HAAGENSEN, M.D.,
AND
ARTHUR PURDY STOUT, M.D.
NEW YORK, N. Y.

FROM THE DEPARTMENT OF SURGERY OF THE PRESBYTERIAN HOSPITAL, AND THE LABORATORY OF SURGICAL PATHOLOGY, COLUMBIA UNIVERSITY, NEW YORK, N. Y.

A NUMBER OF INTERESTING STUDIES of the rare and highly specialized tumor-form, known most commonly as synovial sarcoma, have appeared in recent years. One might expect that a clear conception of the pathology, degree of malignancy, clinical course and results of treatment could be gained by a perusal of these papers. It is distressing to find that this is not so, chiefly because a very considerable number of cases have been reported as synovial sarcomas which were not such, but, in reality, xanthomatous giant cell tumors, tumor-like hyperplasias of the synovial tissues or other benign lesions curable by simple excision. Thus, the apparent cure rate has been made higher than is in fact the truth. It has seemed timely, therefore, to undertake a new study in order to obtain more accurate information.

The procedure has been first to obtain confirmation of the mesothelial nature of the neoplasm by making tissue culture studies of three cases (Nos. 98, 99 and 101). This work is reported elsewhere (Murray, Stout and Pogogeff, ANNALS OF SURGERY, p. 843, this issue), and leaves no doubt about the specialized characteristics of the tumor cells. The three tumors from which these cultures were obtained all had very striking histologic characteristics. They were composed of an inextricable admixture of mesothelial cells which often lined slits or tubes and secreted a mucicarminophilic substance, with strands of active, hyperchromatic fibrosarcoma-like cells associated with reticulin fibers. The relative amounts of these two cell-forms varied enormously, but both of them were always present. It was determined to regard these as the histologic features characterizing this tumor.

With this in mind, cases reported as synovioma, synovial sarcoma, or by some related term, were reexamined and those which did not fulfill our criteria were rejected. This screening yielded 95 cases, to which we add nine additional previously unreported examples, four of them from the Presbyterian Hospital and five from other sources.

An evaluation of the information gleaned from this critically selected group has yielded information of clinical value. Males preponderate in the proportion of 3:2 (males 62, females 41, sex unknown 1). Reference to Chart 1 will show that although this tumor may develop at any age, it is much more frequently found in early adult life than at any other time. The mean age of the 103 patients whose age is known was 32 years.

As is the fact with many bone and joint lesions, synovial sarcomas develop most frequently in the region of the knee joint—nearly half of the tumors have been found in that region. The distribution is as follows: Lower extremity

82 (79 per cent) cases (hip 2, groin 2, buttock 1, thigh 7, knee 49, lower leg 1, ankle 9, foot 10, great toe 1); upper extremity 22 (21 per cent), (axilla 1, elbow 9, forearm 1, wrist 4, hand 3, fingers 4).

It should be pointed out that, whereas, these tumors are composed almost certainly of mesothelial cells, it is very questionable whether or not they are derived from the normal lining cells of joints, tendon sheaths, and bursae, because the tumors are usually outside of these structures although often in close proximity to them. Even when the tumors grow to a relatively large size, it is very rare for the actual lining of joint or tendon sheath to be

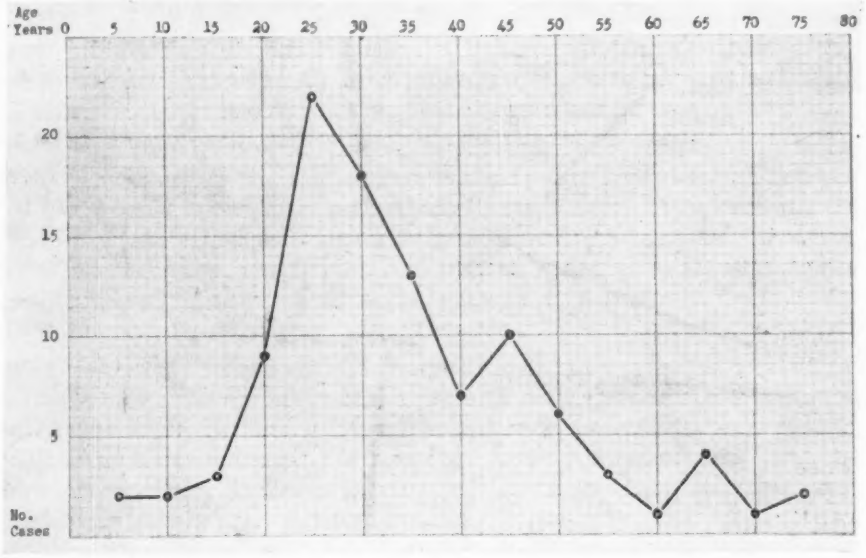


CHART I

Quinquennial Age Distribution of Synovial Sarcomas

affected. Thus, among Briggs' (1942) nine cases only one (Case 88 of this series) involved the synovia, and in our own group of nine cases only one (Case 101) actually involved a synovial membrane. In contradistinction to this, the synovial hyperplasias, giant cell tumors, hemangiomas and other nonmalignant lesions almost always involve the synovial tissues themselves.

The initial symptom of the synovial sarcoma is usually pain. According to Lazarus and Marks (1943) this is preceded in about 25 per cent of cases by a history of trauma. They felt that this was too small to have any etiologic significance, and with this we agree. The pain is often present for a long time, sometimes for several years, before a tumor is noted. The symptoms are so chronic that in a number of these patients the knee has been explored with the provisional diagnosis of internal derangement of the joint. In others the lesion has been mistaken for tuberculosis or for some form of arthritis. The mean duration of symptoms when the patient came for treatment in the 98 cases in which this information was available, was 2.6 years.

The total duration of the disease is correspondingly prolonged. Forty-seven of the patients are known to have died, and in 42 the total duration of disease from the onset of the first symptom to death is stated. It varied from five months to 16 years, the mean total duration being 5.7 years. Only three patients in the group of 104 have been clinically cured for more than five years after treatment. These are cases 33, 83, and 97, which were reported without evidence of tumor six, seven and eight years, respectively. The duration of the disease in the clinically cured cases does not, therefore, influence to any appreciable degree the conclusion derived from the fatal cases that synovial sarcoma is among the more slow growing of the malignant neoplasms.

Although the disease apparently remains localized for several years, metastases eventually manifest themselves in the great majority of cases. Even though the follow-up data are often incomplete in this collection of cases, metastases were recognized in 43 of the 47 patients who died, while seven others who were still alive also had them. The distribution in these 50 patients suggests that although the blood stream is the usual route for metastases, they are occasionally carried *via* the lymphatics to the regional nodes. The recorded sites of involvement were: Lungs 43, lymph nodes 12 (inguinal 7, axillary 4, iliac 1), skin 2, abdomen 1, bones 1, brain 1, generalized 2.

Gross Pathology.—The morphologic characteristics of these tumors are quite uniform. Starting from a focal point they grow chiefly by expansion so that they are circumscribed but as they also infiltrate there is no true capsule and they are more or less adherent to surrounding structures. The gross tumor is nodular and is moulded by the density and resistance of the tissues within which it grows. Its firmness depends upon the relative content of its fibrosarcomatous element, whether or not there is calcification or ossification, and upon the amount of degeneration. When cut open the exposed tumor tissue is basically a very pale creamy-pink like the majority of sarcomas but this is generally mottled with reds and yellows from hemorrhage and degeneration. Some of the tumors are quite hard in places where fibrosis and calcification has occurred. They are generally found close to, or adherent to, a joint, tendon sheath or bursa, but it is seldom that they project into the synovial cavity and some tumors, particularly those arising in the thigh, do not appear to be demonstrably connected with any of these structures.

Histopathology.—The synovial sarcomas are always compounded of two elements both of which are neoplastic and as inseparable as the lining cells of joint, tendon sheath or bursa and the supportive tissue upon which these cells rest. These two may be designated as the fibrosarcomatous element and the synovial element. If one studies a number of different tumors as well as many parts of the same tumor, it becomes apparent that there are almost infinite variations not only in the relative proportions of the two elements with respect to one another but also in the degree of differentiation of the two types

of tissue in the same and different tumors. Always, however, both types are present in some part of the tumor, inextricably intermingled one with the other. One can best study these tumors by using some silver connective tissue fiber stain because of a basic difference between the two tissue types. The fibrosarcomatous elements are always furnished with reticulin fibers which will be blackened by the silver while the synovial elements are always free from fibers. Thus, with a silver stain the relative proportions of the two elements are distinguishable at a glance no matter what the stage of differentiation. Both cell types are found in a number of different guises with varying degrees of differentiation.

The *synovial* elements repeat in an atypical fashion the appearance of the normal lining cells of joints, tendon sheaths and bursae when irritated, or in the embryonal state. Thus, they may appear as solid bands or masses of elongated swollen spindle-shaped cells (Fig. 4), or with slits or spaces among them. If spaces form, the cells lining them may remain relatively unchanged or they may assume a cuboidal (Fig. 3) and sometimes a tall columnar shape (Fig. 7). If cuboidal they may heap up and form papillary projections (Fig. 1). Regardless of their shape and relationship to spaces, the cells often contain droplets of a material staining red with mucicarmine, which we may assume is hyaluronic acid, since this is the mucin-like material formed by synovial cells.

The *fibrosarcomatous* elements surround and enclose the synovial elements wherever they are present. They may be extremely inconspicuous and resemble a mere supportive framework (Fig. 5) or in some areas they may dominate the field to the exclusion of the synovial elements (Fig. 6). Generally the cells are hyperchromatic spindles accompanied by reticulin fibers and they form bands or cords (Fig. 6). Variations from this are the formation of bizarre forms or cuboidal cells when differentiation is poor. On the other hand, there may be areas in which differentiation is so good that adult fibrocytes and collagen fibers predominate. Calcification may occur in such areas or it may sometimes be found where there is no marked fibrosis (Fig. 1). When differentiation is good in a fibrosarcomatous area the synovial elements of the same area usually show a rather high grade of differentiation (Fig. 1). The diagnosis of these tumors histologically is generally easy if one is careful to take a number of sections from different areas for in some of them the characteristic features are sure to appear. A single biopsy may, however, fail to show both elements. The only neoplasms with which it may be confused if both elements are found are the hemangio-endothelioma and the chorionepithelioma. The diagnostic feature which will surely distinguish the synovial sarcoma from these two is the ability of its synovial cells to secrete a mucicarminophilic substance. Neither of the other two are capable of doing this. There is one other lesion of joints which has been confused with synovial sarcoma. This is the formation of a tumor mass within the joint made up of vascular inflammatory and fibroblastic tissue associated with a marked new formation of slit-like spaces lined

with synovial cells. Such lesions closely resemble the synovial sarcomas but they differ in one important respect; neither the synovial cells nor the stromal cells show the morphologic changes which permit one to recognize them as neoplastic. At most, they are hyperplastic. Such tumors, of which we have one example from the knee joint of a 17-year-old girl, might be called benign synoviomas if they could be classified as true neoplasms, but it does not seem proper to suggest this if, as is probable, they are purely inflammatory hyperplasias. As previously stated, the giant cell xanthomatous tumors and the hyperplastic tumors have been included in some reported groups of synovial sarcomas. We do not agree with this and believe that only those cases showing the features above described should have the term applied to them.

Case 1.—(Table I—No. 96). History No. 23151: J. R., a married woman, age 37, came to the Presbyterian Hospital, August 24, 1915, complaining of a tumor in the right popliteal region. Five years previously she had begun to have pain in this region. It was severe enough to keep her awake at night. Four years previously a swelling was noted in the popliteal region, and the pain gradually disappeared. The tumor grew slowly and continuously. Eight months before admission it had become tender, but was otherwise painless. She had had six children, the most recent eight months previously, and she was still lactating on admission to the hospital. There was an oval tumor in the right popliteal region, extending downwards into the calf. It was firm, elastic, and was not tender. It did not move when the calf muscles were contracted. It measured 15 x 10 x 5 cm. The skin over it was normal except for several dilated superficial veins. The lungs were described as clear, but no roentgenologic examination was made preoperatively. At operation (Dr. Hugh Auchincloss), August 25, 1915, a long vertical incision was made over the tumor. It seemed to be encapsulated, and rather soft and hemorrhagic. An attempt was first made to dissect it out from the tissues which surrounded it, but the delicate capsule was repeatedly torn, and the attempt was finally abandoned when the dissection had progressed to the point where it was seen that the internal popliteal nerve could not be freed from the lower pole of the tumor. An amputation just above the knee joint was then performed. On the third day postoperative the patient began to have an elevated temperature, ranging between 101° and 103° F., and complained of pain in her anterior chest. Signs of irregular patchy consolidation over both sides of the chest posteriorly developed, and she began to cough. A roentgenogram showed a number of rounded shadows, some of them as large as five centimeters in diameter, scattered throughout both lung fields. They were beyond doubt metastases. The patient's elevated temperature gradually subsided, her chest pain decreased, and her stump seemed to be healing satisfactorily, until the sixteenth day after operation, when she complained of severe pain in her chest. The next morning she suddenly developed severe dyspnea and cyanosis, and died within half an hour. No autopsy was obtained, but it was presumed that she died of a massive pulmonary embolus.

Microscopically, the fibrosarcomatous elements predominate, and vary tremendously from very fibrous calcified areas to very poor differentiation with round cells. Slits are infrequent. Some are lined with flattened cells, others with cuboidal and occasionally with columnar cells. No mucicarminophilic material demonstrated (Fig. 1).

Case 2.—(Table I—No. 97). History No. 462118: C. S., a 27-year-old pipefitter, came to the Presbyterian Hospital, August 21, 1935, complaining of a tumor of the right elbow. Four years previously he was cranking his car when the engine backfired and he felt something slip in his right elbow. It was painful and slightly swollen for a few days but these symptoms soon disappeared. During the next six months the elbow became increasingly stiffened. He went to a New York hospital where he was

No.	Author	Age	Sex	Site	Duration	Primary Amputation	Local Excision	Local Recurrence	Secondary Amputation	Metastasis	Result	Total Duration

No.	Author	Age	Sex	Site	Duration	Primary Amputation	Local Excision	Local Recurrence	Secondary Amputation	Metastasis	Result	Total Duration
1	Marsh	21 yrs.	M	Knee	14 mos.		+ + + +	2.5 yrs.	+		?	
2	Hannemuller	44 yrs.	M	Ankle	8 mos.		+				?	
3	Lejars, *et al.*	22 yrs.	M	Knee	3.5 yrs.		+ + +	Repeated	+		?	
4	Chenot, *et al.*	38 yrs.	F	Foot	8 mos.		+				?	
5	Faccini	38 yrs.	M	Knee	8 yrs.		+		Soon after excision		Well 1 yr.	
6	Smith	?	?	Thigh	?		+			Lungs, ing. nodes	Died	
7	Smith	24 yrs.	F	Thigh	8 mos.		+	2 mos.		Lungs	Died	3 yrs.
8	Smith	35 yrs.	M	Knee	5 mos.		+	Soon	+	Lungs	Died	2.5 yrs.
9	Wegelin	28 yrs.	M	Knee	3 mos.		+				Well 6 mos.	
10	Tavernier	23 yrs.	F	Knee	12 mos.		+ +	Soon			?	
11	Prym	66 yrs.	F	Knee	7 yrs.		+ +	7 mos.	+	Groin	Died	9 yrs.
12	Wagner	15 yrs.	F	Ankle	6 yrs.		+				Well 1 yr.	
13	Diez	33 yrs.	F	Knee	5 yrs.		+				?	
14	Sabrazès, *et al.*	18 yrs.	F	Popliteal	5 yrs.		+	2.5 yrs.	+	Lungs, ax. nodes	Died	10 yrs.
15	Sabrazès, *et al.*	50 yrs.	M	Elbow	5 yrs.					Lungs, axilla	Died	
16	Hohenthal	22 yrs.	M	Knee	3 yrs.		+			Lungs	Died	8 yrs.
17	Zwahlen	22 yrs.	F	Forearm	2 yrs.		+ +	2 yrs.	+	Lungs	Died	8 yrs.
18	Zwahlen	16 yrs.	M	Ankle	1 yr.		+	14 mos.	+	Lungs	Died	3.5 yrs.
19	Fievez	59 yrs.	F	Ankle	13 yrs.	Late in disease					?	
20	Bonne, *et al.*	25 yrs.	F	Knee	10 mos.						Living	
21	Hodgson, *et al.*	28 yrs.	M	Knee	3 mos.					Skin, ing. nodes	Died	7 mos.
22	Adair	24 yrs.	M	Ankle	6 mos.		+	Soon		Lungs	Died	2.5 yrs.
23	Adair	47 yrs.	M	Knee	2 yrs.		+	18 mos.		Lungs	Died	3 yrs.
24	Adair	9 mos.	M	Knee	7 mos.		+ +	1 mo.			Well 3.5 yrs.	
25	Knox	22 yrs.	F	Elbow	3 yrs.		+	15 mos.	+	Shoulder, lungs	Died	10 yrs.
26	Knox	33 yrs.	M	Popliteal	6 mos.	Biopsy foll. by amputation				Lungs	Died	3 yrs.
27	Knox	24 yrs.	M	Foot	2.5 yrs.		+		Soon after excision	Lungs	Living 4 yrs.	
28	Black	36 yrs.	M	Thumb	3 yrs.		+				Well 6 mos.	
29	Coley, *et al.*	45 yrs.	M	Finger	7 mos.		+		+		?	
30	Coley, *et al.*	35 yrs.	M	Sole of foot	3 yrs.				Following radiation	Lungs	Died	4 yrs.
31	Coley, *et al.*	22 yrs.	F	Dorsum hand	7 yrs.		+	12 mos.	+	Lungs	Died	8.3 yrs.
32	Coley, *et al.*	35 yrs.	F	Knee	8 yrs.		+				Well 18 mos.	
33	Coley, *et al.*	12 yrs.	F	Knee	1 yr.		+		Following radiation		Well 6 yrs.	
34	Coley, *et al.*	64 yrs.	M	Foot	5 mos.		+				Well 3.5 yrs.	
35	Coley, *et al.*	27 yrs.	M	Palm hand	6 mos.		+ +				Living 16 mos.	
36	Coley, *et al.*	16 yrs.	F	Knee	6 mos.		+ + +	3 mos.			Well 2.5 yrs.	
37	Coley, *et al.*	45 yrs.	F	Great toe	1 mo.		+ +	2 mos.			Well 1.5 yrs.	
38	Coley, *et al.*	45 yrs.	M	Knee	2.7 yrs.		+ + +	5 mos.			Recurrence	
39	Coley, *et al.*	29 yrs.	F	Popliteal	2 yrs.		+ +	2 yrs.		Lungs	Died	9 yrs.
40	Coley, *et al.*	45 yrs.	F	Dorsum foot	1 yr.		+ +	Prompt			Persisting disease	
41	Fehr	22 yrs.	F	Dorsum wrist	3 yrs.		+	Soon	+	Lungs	Died	7 yrs.
42	Fehr	17 yrs.	M	Ankle	1 yr.		+ +	2 mos.	+	Lungs, axilla	Died	6 yrs.
43	Fehr	54 yrs.	M	Elbow	7 yrs.		+			Lungs, brain	Died	10 yrs.
44	Fehr	18 yrs.	M	Thumb	1 yr.		+ +	5 mos.			Well 1 yr.	
45	Cabot Case No. 24321	25 yrs.	M	Knee	5 yrs.		+	Soon	+		?	
46	Berger	30 yrs.	M	Thigh	6 mos.		+	5 mos.			?	
47	Berger	38 yrs.	M	Thigh	6 mos.		+			Ing. nodes, abdomen, lungs	Died	1 yr.
48	Berger	26 yrs.	M	Axilla	3 mos.		+			Lungs	Died	2 yrs.
49	Berger	75 yrs.	F	Dorsum wrist	7 yrs.		+	3 weeks	+		?	
50	von Verebély	51 yrs.	M	Knee	9 yrs.		+ +	6 mos.		Lungs	Died	10 yrs.
51	Klages	28 yrs.	M	Hip	4 yrs.		+ +	12 mos.			Died	7 yrs.
52	Cabot Case No. 25312	71 yrs.	M	Popliteal	1 yr.		+	8 mos.		Lungs	Died	2 yrs.
53	Hutchison, *et al.*	28 yrs.	F	Knee	2 yrs.		+	22 mos.		Lungs	Died	7 yrs.
54	Schie	32 yrs.	M	Hip	3 mos.		+	1 mo.		Lungs	Died	5 mos.
55	Silfverskiold	23 yrs.	M	Wrist	6 mos.		+ +	18 mos.		Lungs	Died	5 yrs.
56	Silfverskiold	43 yrs.	M	Foot	4 yrs.		+		Soon after excision		Well 3 mos.	
57	Silfverskiold	53 yrs.	F	Foot	4 yrs.		+				Well 10 mos.	
58	Aitkin	21 yrs.	M	Knee	2 yrs.		+	9 mos.	+	Lungs	Died	
59	Leichner, *et al.*	10 yrs.	F	Buttock			+			Lungs	Died	
60	De Santo, *et al.*	30 yrs.	M	Elbow	6 mos.		+			Ax. nodes	Living 14 mos.	
61	De Santo, *et al.*	63 yrs.	M	Elbow	2 yrs.		+				Well 11 mos.	
62	De Santo, *et al.*	50 yrs.	F	Elbow	10 yrs.		+ +	6 mos.			?	

36	Coley, *et al.*		F										
37	Coley, *et al.*	45 yrs.	F	Great toe	1 mo.	+	+		2 mos.			Well 1.5 yrs.	
38	Coley, *et al.*	45 yrs.	M	Knee	2.7 yrs.	+	+	+	5 mos.			Recurrence	
39	Coley, *et al.*	29 yrs.	F	Popliteal	2 yrs.	+	+		2 yrs.		Lungs	Died	9 yrs.
40	Coley, *et al.*	45 yrs.	F	Dorsum foot	1 yr.	+	+		Prompt			Persisting disease	
41	Fehr	22 yrs.	F	Dorsum wrist	3 yrs.	+			Soon	+	Lungs	Died	7 yrs.
42	Fehr	17 yrs.	M	Ankle	1 yr.	+	+		2 mos.	+	Lungs, axilla	Died	6 yrs.
43	Fehr	54 yrs.	M	Elbow	7 yrs.	+					Lungs, brain	Died	10 yrs.
44	Fehr	18 yrs.	M	Thumb	1 yr.	+	+		5 mos.			Well 1 yr.	
45	Cabot Case No. 24321	25 yrs.	M	Knee	5 yrs.	+			Soon	+		?	
46	Berger	30 yrs.	M	Thigh	6 mos.	+			5 mos.			?	
47	Berger	38 yrs.	M	Thigh	6 mos.	+					Ing. nodes, abdomen, lungs	Died	1 yr.
48	Berger	26 yrs.	M	Axilla	3 mos.	+					Lungs	Died	2 yrs.
49	Berger	75 yrs.	F	Dorsum wrist	7 yrs.	+			3 weeks	+		?	
50	von Verebély	51 yrs.	M	Knee	9 yrs.	+	+		6 mos.		Lungs	Died	10 yrs.
51	Klages	28 yrs.	M	Hip	4 yrs.	+	+		12 mos.			Died	7 yrs.
52	Cabot Case No. 25312	71 yrs.	M	Popliteal	1 yr.	+			8 mos.		Lungs	Died	2 yrs.
53	Hutchison, *et al.*	28 yrs.	F	Knee	2 yrs.	+			22 mos.		Lungs	Died	7 yrs.
54	Schie	32 yrs.	M	Hip	3 mos.	+			1 mo.		Lungs	Died	5 mos.
55	Silfverskiold	23 yrs.	M	Wrist	6 mos.	+	+		18 mos.		Lungs	Died	5 yrs.
56	Silfverskiold	43 yrs.	M	Foot	4 yrs.	+				Soon after excision		Well 3 mos.	
57	Silfverskiold	53 yrs.	F	Foot	4 yrs.	+						Well 10 mos.	
58	Aitkin	21 yrs.	M	Knee	2 yrs.	+			9 mos.	+	Lungs	Died	
59	Leichner, *et al.*	10 yrs.	F	Buttock		+					Lungs	Died	
60	De Santo, *et al.*	30 yrs.	M	Elbow	6 mos.	+					Ax. nodes	Living 14 mos.	
61	De Santo, *et al.*	63 yrs.	M	Elbow	2 yrs.	+						Well 11 mos.	
62	De Santo, *et al.*	50 yrs.	F	Elbow	10 yrs.	+	+		6 mos.			?	
63	De Santo, *et al.*	26 yrs.	F	Thigh	9 mos.	+			3 mos.			?	
64	De Santo, *et al.*	23 yrs.	M	Knee	2.5 yrs.	Semi. cart. excised				+	Lungs	Died	7.2 yrs.
65	De Santo, *et al.*	22 yrs.	M	Knee	3 yrs.	+	+		3 mos.			Well 1 yr.	
66	De Santo, *et al.*	37 yrs.	F	Knee	6 mos.	Twice explored				+	Lungs	Living	
67	De Santo, *et al.*	24 yrs.	M	Knee	6 yrs.	+			11 mos.	+	Lungs	Died	10 yrs.
68	De Santo, *et al.*	34 yrs.	F	Wrist	6 yrs.	+						Well 9 mos.	
69	De Santo, *et al.*	35 yrs.	M	Knee	10 yrs.	+	+	+	12 mos.	+	Lungs	Died	16 yrs.
70	De Santo, *et al.*	25 yrs.	M	Knee	8 yrs.	+	+		14 mos.	+	Generalized; lungs	Died	11 yrs.
71	De Santo, *et al.*	32 yrs.	F	Finger	6 mos.	+				+		Well 18 mos.	
72	De Santo, *et al.*	48 yrs.	M	Popliteal	1 mo.	+	+		3 mos.			Well 2 yrs.	
73	De Santo, *et al.*	46 yrs.	M	Popliteal	1 mo.	+	+		9 mos.	+		Well 1 yr.	
74	De Santo, *et al.*	40 yrs.	M	Proximal lower leg	2 yrs.	+					Lungs	Died	3.5 yrs.
75	De Santo, *et al.*	45 yrs.	M	Elbow	1 mo.	+					Lungs, bones, skin, abdomen	Died	1.5 yrs.
76	Ioffe, *et al.*	28 yrs.	M	Knee	2.5 yrs.	+						Died	4.5 yrs.

71	De Santo, *et al.*	32 yrs.	F	Finger	6 mos.		+		+		Well 18 mos.		
72	De Santo, *et al.*	48 yrs.	M	Popliteal	1 mo.		+ +	3 mos.			Well 2 yrs.		
73	De Santo, *et al.*	46 yrs.	M	Popliteal	1 mo.		+ +	9 mos.	+		Well 1 yr.		
74	De Santo, *et al.*	40 yrs.	M	Proximal lower leg	2 yrs.		+			Lungs	Died	3.5 yrs.	
75	De Santo, *et al.*	45 yrs.	M	Elbow	1 mo.		+			Lungs, bones, skin, abdomen	Died	1.5 yrs.	
76	Jaffe, *et al.*	28 yrs.	M	Knee	2.5 yrs.		+				Died	4.5 yrs.	
77	Jaffe, *et al.*	24 yrs.	M	Foot			+				Died		
78	Jaffe, *et al.*	20 yrs.	F	Knee	2 yrs.		+ + +	13 mos.	+		Well 3.5 yrs.		
79	Jaffe, *et al.*	15 yrs.	M	Ankle	3 yrs.		+				?		
80	Votta	63 yrs.	M	Knee	3 mos.		+	2 mos.	+	Lungs	Died	9 mos.	
81	Fisher	20 yrs.	F	Popliteal	Months		+ +	6 mos.	+	Lungs	Died	3 yrs.	
82	Briggs	17 yrs.	F	Ankle	4 mos.		+	Few mos.		Ing. nodes, lungs	Died	5 yrs.	
83	Briggs	45 yrs.	F	Knee	4 yrs.		+				Well 7 yrs.		
84	Briggs	30 yrs.	F	Sole of foot			+ +	2.5 yrs.	+	Ing. nodes, lungs	Died	8 yrs.	
85	Briggs	22 yrs.	F	Ankle	2.5 yrs.		+				Well 1.5 yrs.		
86	Briggs	45 yrs.	M	Thigh	3 yrs.		Exploratory dissection		Immediate		Well 2.5 yrs.		
87	Briggs	17 yrs.	M	Elbow	4 mos.		+ +				Well 4.5 yrs.		
88	Briggs	35 yrs.	F	Knee	7 yrs.	Biopsy foll. by amputation				Lungs	Died	11 yrs.	
89	Briggs	25 yrs.	M	Popliteal	3 mos.		+ +			Ing. nodes, lungs	Died	1 yr.	
90	Briggs	27 yrs.	M	Popliteal	5 weeks		+ +	12 mos.			Recurrence		
91	Snyder	35 yrs.	F	Knee	2 yrs.		+		+		Well 1.5 yrs.		
92	Stanford, *et al.*	16 yrs.	M	Knee	3 mos.	Biopsy foll. by amputation				Lungs	Living 5 mos.		
93	Eveleth, *et al.*	61 yrs.	F	Knee	4 yrs.					Ing. and iliac lymph nodes	?		
94	Lazarus, *et al.*	30 yrs.	M	Hand	2.2 yrs.		+ +				Well 2 yrs.		
95	Lazarus, *et al.*	47 yrs.	F	Knee	9 mos.		+ +			Diffuse nodes and abdomen	Living 1 yr.		
96	Columbia Univ.	37 yrs.	F	Popliteal	5 yrs.		Exploratory dissection		Immediate		Operative death	5 yrs.	
97	Columbia Univ.	27 yrs.	M	Elbow	4 yrs.	Biopsy foll. by amputation					Well 8 yrs., 8 mos.		
98	Columbia Univ.	19 yrs.	M	Groin	15 mos.		+			Lungs	Died	5.4 yrs.	
99	Columbia Univ.	44 yrs.	M	Thigh	1 yr.		Exploratory dissection		Soon after exploration		Well 15 mos.		
100	Columbia Univ.	10 yrs.	M	Groin							Died	6 yrs.	
101	Columbia Univ.	5 yrs.	M	Knee	8 mos.		+ + +		+		Well 3.4 yrs.		
102	Columbia Univ.	28 yrs.	M	Knee	3 mos		+			Lungs	Living 3 mos.		
103	Columbia Univ.	29 yrs.	F	Foot	5 yrs.		+	4 mos.			Living 4 mos.		
104	Columbia Univ.	31 yrs	F	Popliteal	8 mos.		+	16 mos			Living 16 mos		

given an anesthetic and the elbow manipulated. The increased freedom of motion did not last long, however, and within a short time his elbow could not be moved more than about ten degrees. Soon after the manipulation the patient noticed a tumor along the lateral border of the elbow. This slowly increased in size. A week before admission to the hospital he jerked his arm and the resulting pain drove him to seek medical advice. Examination showed the right forearm in about 130° of flexion. There was motion by measurement between 128° and 92°. Supination was full but slightly painful. Only about one-third of pronation was possible. Over the origin of the extensors of the

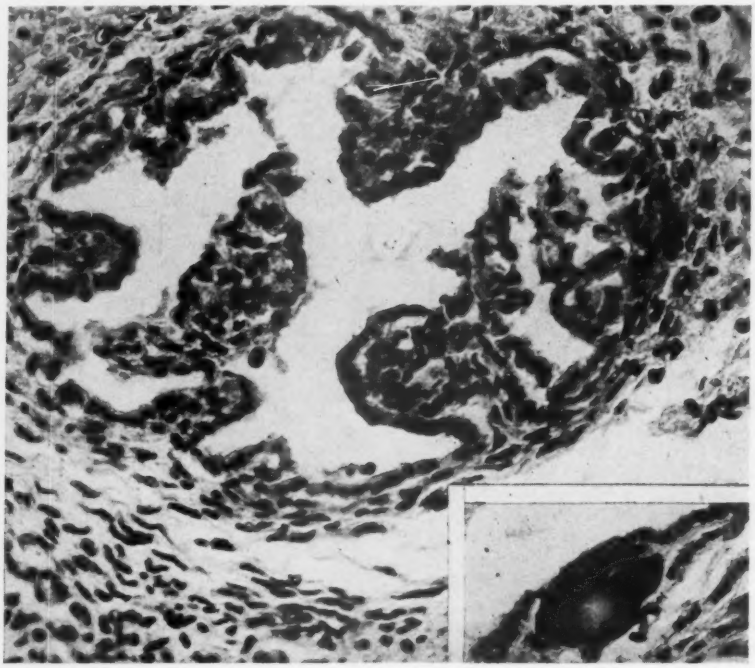


FIG. 1.—Case 1 (Table I—No. 96): Synovial sarcoma of right popliteal region. Photomicrograph (× 410); hematoxylin and eosin stain. A well differentiated synovial tumor structure in which villous processes have been formed. The inset shows an area of calcification in a villous process.

forearm and wrist there was a firm tumor which moved with muscle contraction. Roentgenograms showed a widening of the humeral metaphysis in the supracondylar region, with a bony spur projecting downward and anteriorly from this portion of the humerus. The findings were those of an old united fracture of the humerus. It was assumed that the tumor was a calcified hematoma. Doctor W. Darrach performed an exploratory operation on September 12, 1935. A soft, encapsulated, fusiform tumor mass, measuring 7 x 4.5 cm., was found lying between the brachioradialis and biceps muscles. The radial nerve entered the upper pole of the tumor and its fibers were seen spreading out over its surface (Fig. 2). An incision, one centimeter in length, was made into the tumor for biopsy, and several small fragments of friable reddish tissue removed. Frozen sections showed a cellular sarcoma. Further histologic study was deemed desirable before deciding upon the form of treatment, and the wound was, therefore, closed in layers. Study of the 24-hour paraffin sections having shown that the tumor was a synovial sarcoma, amputation through the shoulder was decided upon. This was performed September 14, 1935. Convalescence was uneventful. When he was last seen eight years and eight months later, in May, 1944, he was well and working as

a photostat operator. A roentgenogram of the chest taken at that time did not show any evidence of metastases.

Microscopically, this is a poorly differentiated tumor in which the synovial elements predominate. Slits are many, but small, and lined with undifferentiated cells (Fig. 3). Some contain droplets of mucoid. In the better differentiated areas, the fibrosarcomatous elements become ordinary fibrous tissue and, clothed with synovial tumor cells, form papillary projections into the enlarged spaces.

Case 3.—(Table I—No. 98). History No. 606261: G. W., a 19-year-old boy, came to the Presbyterian Hospital, April 5, 1940, complaining of a recurrent tumor of the left femoral region. Fifteen months previously, while fencing, he had first noted a small tumor nodule in the left femoral region. On the evening of the same day on which he discovered the tumor, severe pain developed in the groin, and he went to his physician. His temperature was found to be elevated, and he was sent to a local hospital. There, on the following day, the mass in the groin was incised and a large amount of "blood

FIG. 2.—Case 2 (Table I—97): Synovial sarcoma of right antecubital fossa. Dissection to show relationship to radial nerve and joint capsule.

and pus" drained. He remained in the hospital 11 days. The wound healed satisfactorily, and after healing was complete no swelling remained. After an interval of ten months, during which he was apparently well, recurrence of the tumor in the femoral region was discovered. It was about the same size as the original tumor, but was painless. After some weeks of indecision, by the doctors he consulted, he was taken to a hospital in another city, where a biopsy was done, and a diagnosis of "fibro-spindle cell sarcoma" was made. The lesion having been considered inoperable, a series of roentgen ray treatments was given. An anterior and a posterior portal were used, each measuring 10 x 15 cm. Treatments were given on January 23, 24, 25, 26, 27, and 29, and on March 19, 20, 21, 22, and 23, 1940. The total dose to the anterior portal was 1944 r., while the posterior portal received 1464 r. The factors used were: 200 kilovolts, 50 cm. skin target distance, and filter of 2 Mm. of copper. The radiation failed to produce any change in the size of the tumor, and the patient was brought to the Presbyterian Hospital for consultation. Examination on admission showed an irregularly-shaped, 5 x 8 cm., firm tumor in the left femoral region below Poupart's ligament. The skin over the femoral region was reddened and tanned, and over the center of the tumor there was a vertical biopsy scar. The tumor gave the impression of being an aggregation of small nodules. It could be moved slightly over the deeper structures of the thigh. A roentgenogram of the chest failed to show any metastases. It was

decided to make certain of the nature of the tumor by another biopsy, and this was undertaken on April 12, 1940. When it was exposed, the tumor seemed to be apparently encapsulated, and was soft and reddish. A small piece was excised and the wound closed. The histologic diagnosis was synovial sarcoma. The tumor was situated so high in the thigh that hip-joint amputation would have been inadequate. A hemipelvectomy was discussed, but the surgeon in charge (Dr. Louis Rousselot) decided against it, and in favor of further radiotherapy. Between April 19 and May 15, 1940, he was treated through two portals, a 10 x 20 cm. anterior one, and a 10 x 10 cm. lateral one. Each received 1900 r. The factors used were 200 kilovolts, 50 cm. skin target distance, filter of 2 Mm. of copper. There was no discernible change in the size of the tumor following irradiation. The patient refused to return for follow-up after six months and

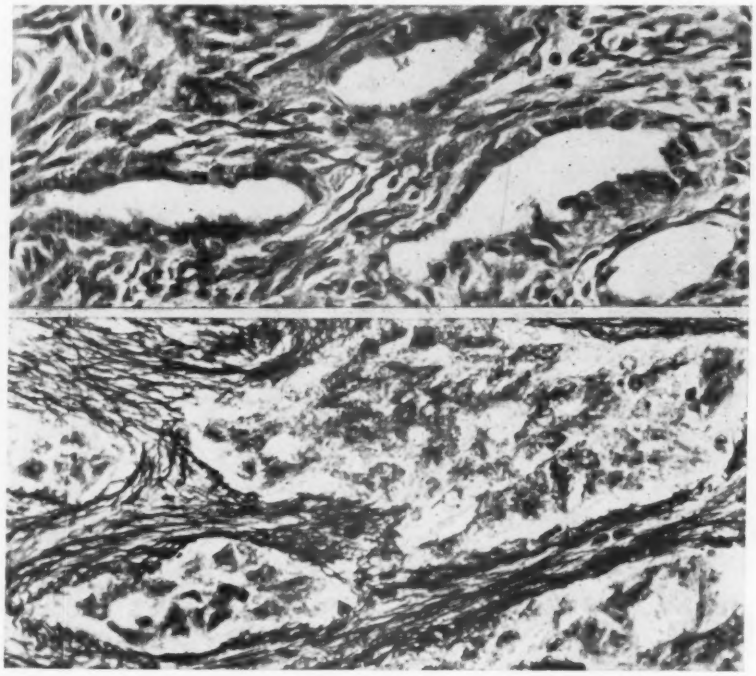


FIG. 3.—Case 2 (Table I—No. 97): Synovial sarcoma of antecubital fossa. Photomicrograph (× 410); hematoxylin and eosin stain above and Laidlaw's silver reticulin stain below. Slits lined by well differentiated synovial tumor cells are scattered through a matrix of spindle-shaped cells accompanied by abundant reticulin fibers.

consulted other physicians. He developed lung metastases, and died in April, 1943, five years and five months after the discovery of the tumor. An autopsy was not obtained.

Microscopically, the biopsy shows undifferentiated synovial and fibrosarcomatous areas, with relatively few slits. Mucoid material is present in many of the synovial cells. The synovial cells lining the slits are usually swollen and rounded, but occasionally elongated (Fig. 4).

Case 4.—(Table I—No. 99). History No. 493264: W. D., a 44-year-old Welsh porter, came to the Presbyterian Hospital, October 27, 1942, complaining of a painful tumor of the left thigh. One year before, while he was helping to lift a truck, the truck slipped and its corner struck him a heavy blow on the left thigh. There was considerable swelling and a large purple area developed in the skin. His physician saw the injury, said there was no fracture, and advised the application of heat.

Several days after the injury a tender, doughy mass was noted in the injured area. This tumor persisted without evident change until he came to the hospital. Examination showed a large, firm, but not hard tumor occupying the middle portion of the vastus medialis and the lower portion of the adductor group of muscles of the left thigh. It was moderately tender and immovable. A second similar, but smaller, tumor was noted in the lower part of the rectus femoris. There was slight atrophy of the thigh but no limitation of motion. Roentgenologic studies of the chest and skeleton showed nothing noteworthy. A tentative diagnosis of hematoma of the thigh was made and, October 28, 1942, an exploratory operation was performed by Dr. F. R. Meleney. A vertical incision was made over the lesion, which was found to be a soft, apparently circumscribed, neoplasm. An attempt was made to enucleate it, but was abandoned

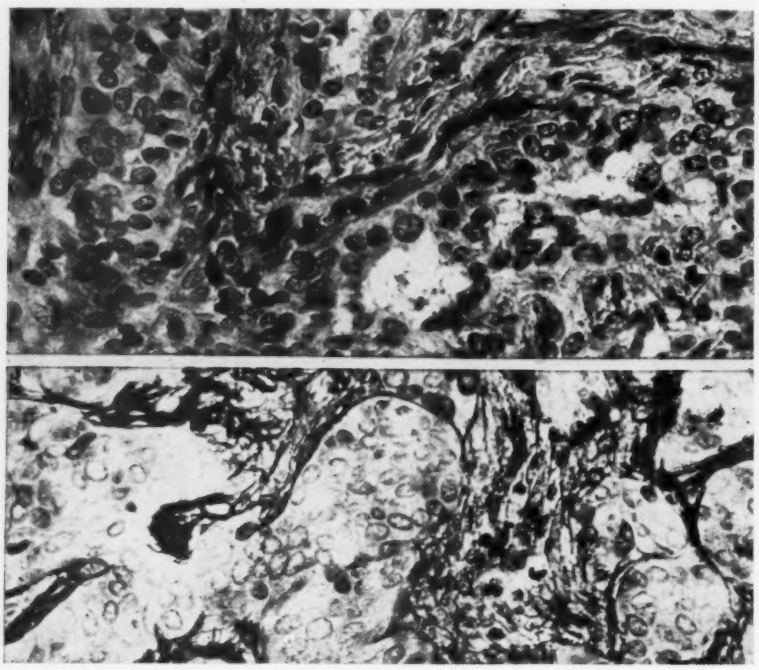


FIG. 4.—Case 3 (Table I—No. 98): Synovial sarcoma of upper anterior femoral region. Photomicrograph (× 410); hematoxylin and eosin stain above and Laidlaw's silver reticulin stain below. The cords of poorly differentiated synovial tumor cells without any fibers among them are separated by slender strands of spindle-shaped cells accompanied by numerous delicate reticulin fibers.

when muscle adjacent to the base of the tumor was found to be infiltrated. A biopsy was then removed, which showed, what was thought to be, a fibrosarcoma. Since permission for amputation had not been obtained the operation was terminated. On November 2, 1942, Doctor Meleney performed a hip joint disarticulation. Recovery was uneventful. In February, 1944, the patient was well and working. The tumor measured 8 x 8 cm.

Microscopically, the tumor is largely fibrosarcomatous and there are big areas without any synovial cells but these are plentiful elsewhere. Differentiation is variable in both parts but usually rather poor. Mucoid material is demonstrated in the slits. The synovial cells vary in shape from cuboidal to low columnar (Figs. 5 and 6).

Case 5.—(Table I—No. 100). P. & S. No. 19873 (from Dr. R. Ball): H. R., a male child, age ten, entered a hospital in Chattanooga, Tenn., in 1932, with a 3-cm.

tumor in the left groin. An aspiration biopsy was done, and it was decided to treat the lesion with roentgenotherapy. The tumor, however, continued to enlarge, and during the following four years attained a massive size. There was much calcification within the growth. Local excision was then attempted, but the tumor could be only partially excised. Death occurred in 1938, about six years after the onset of the disease.

Microscopically, the fibrosarcomatous elements predominate in some areas, and in these there is calcification. Elsewhere synovial cells dominate the picture. Spaces are formed occasionally with papillary infoldings and mucoid material. Differentiation is poor and no columnar cells are formed.

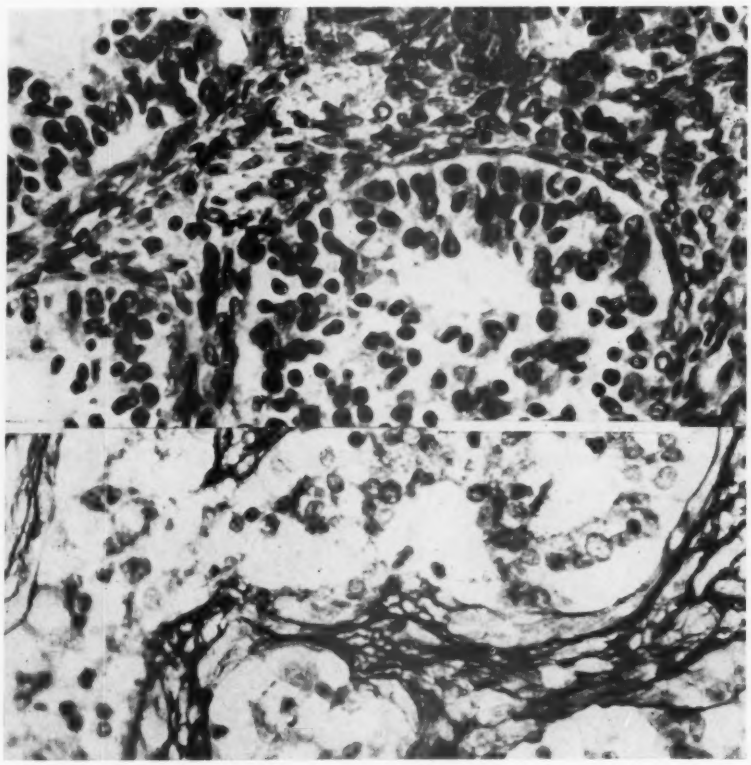


FIG. 5.—Case 4 (Table I—No. 99): Synovial sarcoma of lower medial portion of left thigh. Photomicrograph (× 410); hematoxylin and eosin stain above and Laidlaw's silver reticulin stain below. Portion of the tumor showing characteristic division into synovial tumor cell structures and fibrosarcoma-like areas.

Case 6.—(Table I—No. 101). P. & S. No. 17842 (from Dr. C. Z. Garber): M. V., —a boy, age five, came to the New York Orthopaedic Dispensary and Hospital in December, 1937, complaining of pain in the left knee. The pain had begun following a blow from a golf club eight months previously. The knee was explored in December, 1937, but nothing more than an hypertrophied fat pad was found. This was excised, but no tumor was found microscopically. Two years later, in January, 1939, three firm nodules, each measuring between 1 and 1.5 cm., were excised from the scar. Pain and tenderness in the knee continued, and it was explored again March 13, 1940, by Dr. A. DeF. Smith. A number of thickened, purplish areas, suggestive of hemangioma, were found in the synovia. The process extended around the cruciate ligaments and into the posterior part of the knee. Frozen section of the tissue removed showed synovial

sarcoma. Roentgenograms of the chest were negative. Doctor Smith, therefore, performed a midthigh amputation on March 22, 1940. There was no evidence of recurrence or metastases when the patient was last seen in August, 1943, three years and five months after amputation, and six years and four months after the initial symptom of the disease.

Microscopically, fibrosarcomatous elements predominate but there are many gland-like spaces lined with tall columnar cells. Mucoid is found in some spaces. Differentiation is generally good (Fig. 7).

Case 7.—(Table I—No. 102). P. & S. No. 18286 (from Dr. R. Forsythe): P. S., a male, age 28, entered the Grasslands Hospital in September, 1940, complaining of a recurrent tumor of the thigh. The original tumor had been present for two or three

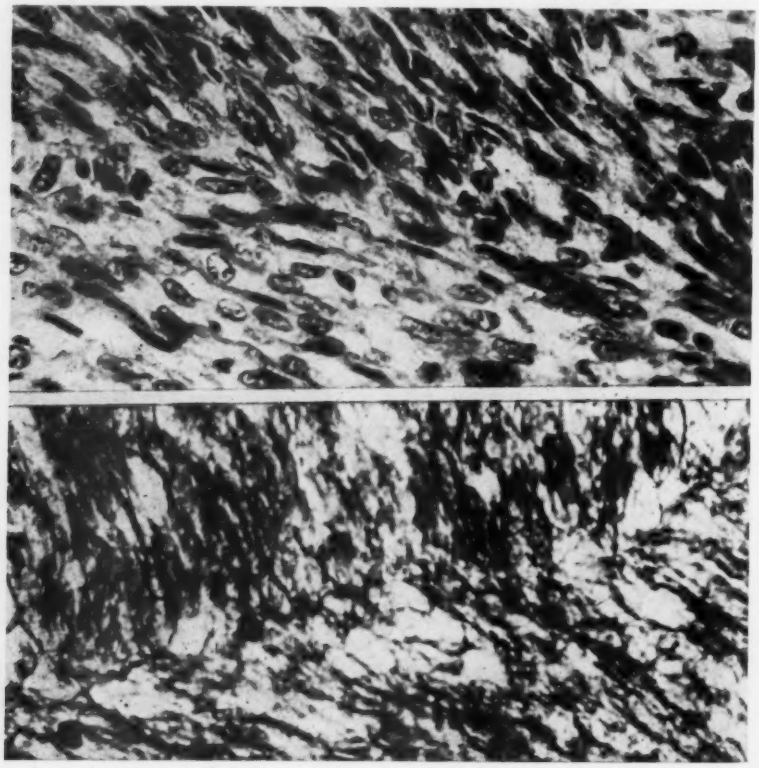


FIG. 6.—Case 4 (Table I—99): Photomicrograph (×410); hematoxylin and eosin stain above and Laidlaw's silver reticulin stain below. Another portion of the same tumor illustrated in Figure 5 to show a pure fibrosarcoma-like area without any differentiated synovial sarcoma cells.

months, when it was excised locally in June, 1940, at the Peekskill Hospital. The recurrent tumor was in the operative scar, on the medial aspect of the proximal portion of the right thigh. Roentgenograms revealed a questionable solitary lung metastasis.

Microscopically, the fibrosarcomatous elements predominate, sometimes with the formation of round instead of spindle cells. There are very few synovial cells but these form spaces and the cells secrete mucoid material.

Case 8.—(Table I—No. 103). P. & S. Nos. 20119 and 20467 (from Dr. Chester Brown): M. D., a white female, age 29, came to the Lincoln Hospital in January, 1942, complaining of a tumor on the lateral aspect of the right foot. The tumor had been first

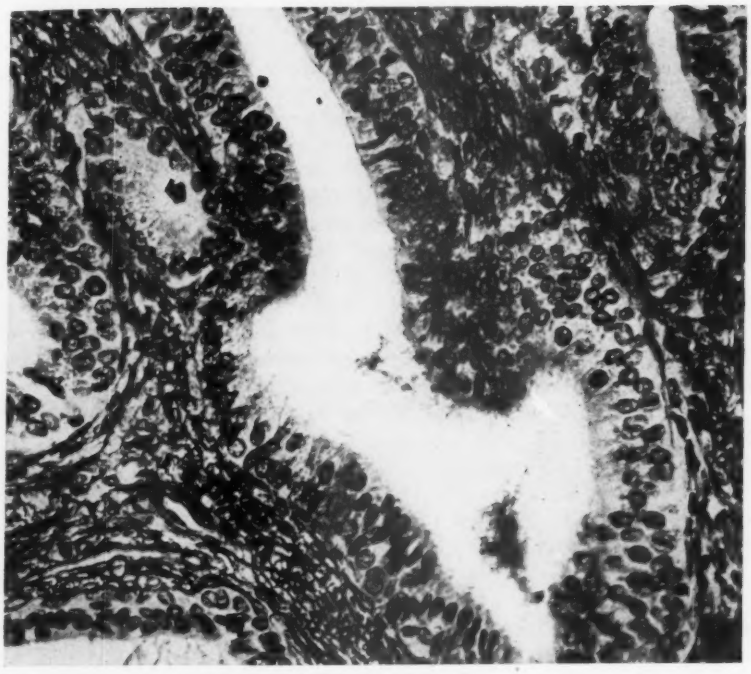


FIG. 7.—Case 6 (Table I—No. 101): Synovial sarcoma of knee joint. Photomicrograph (× 410); Laidlaw's silver reticulin stain. Synovial tumor cells of columnar shape line the cavities. Reticulin fibers abundant but limited strictly to the tissue outside of the synovial cells.

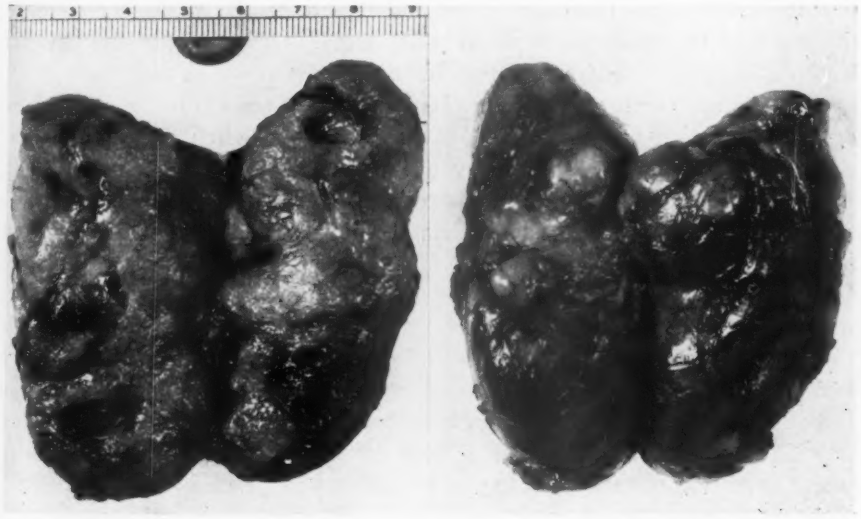


FIG. 8.—Case 9 (Table I—No. 104): Synovial sarcoma of popliteal region. (Photograph by courtesy of Dr. G. H. Klinck).

noticed five years previously, in 1927, as a "small pimple" situated on the lateral side of the base of the fifth toe. It gradually enlarged, extending on to both the dorsal and plantar surfaces of the foot. Growth had been more rapid during the three months prior to admission to the hospital, the period corresponding to the duration of her third pregnancy. She had had two previous children, ages four and two, respectively. The tumor had ulcerated a month before her admission. An aspiration biopsy had been attempted at another hospital. Examination showed a large fungating, papillary, bleeding tumor involving the dorsum of the right foot in the region of the fifth metatarsophalangeal joint, growing down between, and spreading apart, the fourth and fifth toes, and extending on to the plantar surface of the foot. The entire tumor measured 10 x 3 cm. Roentgenograms showed pressure erosion of the fifth metatarsal bone. On January 8, 1942, an attempt was made to excise the tumor locally, but it was found that it could not be completely removed. Four months later recurrence was evident.

Microscopically, fibrosarcomatous areas predominate, with formation of some rounded cells, and, differentiation, very variable and peculiar. In only two, out of many, sections do synovial cells appear but thse are well differentiated and line cavities containing mucoid material.

Case 9.—(Table I—No. 104). P. & S. No. 21614 (from Dr. G. H. Klinck and Dr. G. A. Clark): K. S., age 31, was admitted to the Samaritan Hospital, Troy, N. Y., because of a tumor of the popliteal region. It had been present for eight months and was painless. On February 1, 1943, the tumor was excised locally. It was encapsulated, but it could not be completely removed (Fig. 8). The patient refused amputation. Sixteen months later there was a local recurrence, six centimeters in diameter.

Microscopically, synovial cells predominate. There are many spaces, some lined with flattened differentiated cells and others with swollen undifferentiated cells. There is some fibrosis. Very little mucoid material is demonstrated.

Treatment.—The situation of synovial sarcoma in a limb, and its tendency to remain localized for a long time, are factors that give the surgeon a great advantage in dealing with it. That he has failed to take advantage of this opportunity is clear from the disastrous record of the treatment used in the series of 104 cases which we have reviewed. Only three of the patients were clinically cured more than five years.

The therapy employed has been of four general types: (1) Radiation alone or in combination with surgery; (2) local excision, often repeated several times; (3) excision, or exploratory operation, with an attempt at excision, followed immediately, or within a short time, by amputation; and (4) biopsy followed shortly by amputation. We will discuss these methods of treatment in order.

Radiation appears to have been singularly futile in this disease. It has often been employed, but five-year cure has not been obtained in a single case in which radiation was the chief reliance. In Case 33 in Table I (Coley and Pierson's Case 8), the patient was well six years after treatment, but the radiation treatment was followed by amputation. We have been unable to find any clear evidence that radiation is even of palliative value. In Case 98, in which intensive radiation aiming at palliation was given in our own clinic, there was no definite benefit from it.

Local excision has been the usual treatment. It was undertaken in 84 of the 104 cases that we have tabulated. One of these patients had four local

excisions, six of them had three, and 35 had two attempts at excision. The tumor was usually shelled out by blunt dissection. Sometimes it was removed in fragments. As with other forms of fully malignant sarcoma, any sort of local excision almost always fails to cure. In this series of synovial sarcomas only one of the patients appears to have been clinically cured by local excision. The details of this case (No. 83, reported by Briggs) are as follows: The patient was a woman, age 45, who had a smooth, soft, 6 x 4 x 4 cm., tumor on the lateral surface of the leg about the level of the head of the fibula. It had been present for four years. At operation, it was found to be well encapsulated and was excised. Postoperative radiation was given. She was well seven years later.

Secondary amputation for recurrence following local excision was carried out in 26 of this group of conservatively treated patients. None was cured. Just as in other forms of malignant sarcoma secondary amputation is usually futile, except as a palliative procedure, when local excision has been tried and has failed.

The third type of treatment used in the cases that we have reviewed was excision, or exploratory dissection with an attempt at excision, followed immediately or within a short time by amputation. Here the surgeon relied on primary amputation for cure, but he unfortunately came to this decision only after he had carried out a considerable dissection of the tumor, thereby increasing the likelihood of metastasis. Cases 5, 27, 33, 56, 86, 96, and 99 were treated in this manner. Only one of these patients appears to have been cured, this was Coley and Pierson's patient (Case 33 in our table, No. 8 in their series), a 12-year-old school girl who had a lemon-sized tumor of one year's duration over the left knee. It was explored and excised, and when the nature of the lesion became apparent from histologic study a course of radiation was administered and the leg was amputated. She was well six years later.

Finally, there was a small group of four cases in which a simple biopsy was done, followed shortly by primary amputation when the malignant nature of the lesion became clear from histologic study (Cases 26, 86, 92, and 97). Although the first three of these patients subsequently developed pulmonary metastases, the fourth, our own patient (Case 97), has been well for eight years. This is the longest survival on record following any form of treatment for synovial sarcoma.

We hope that it is more than a coincidence that the longest cure of synovial sarcoma has been obtained by the most radical surgical attack, for it is our firm belief that this is the rational therapy. In a disease in which the results have been as bad as in this one, the surgeon must take courage and use the most radical therapy available. This is a carefully limited biopsy and a high immediate amputation.

The biopsy must be done because it is impossible to diagnose synovial sarcoma, as well as a variety of other deep soft-part tumors, from the clinical picture alone. Moreover, the biopsy must be an incisional biopsy and not an

aspiration biopsy, for the diagnosis of these tumors rests to a considerable extent upon the histologic architecture of the lesion. Diagnosis based upon cytology alone is uncertain. In carrying out the incisional biopsy the dissection should be as limited as possible. It is our preference to make a two- or three-centimeter incision through the skin directly over the tumor. The incision is carried down through the subcutaneous tissue and fascial planes until the periphery of the neoplasm is reached. A small wedge of the tumor, measuring two or three millimeters in width and about one centimeter in length and depth, is then excised with a sharp knife. After careful hemostasis the capsule of the tumor and the fascial planes and skin are closed in layers with interrupted silk. We do not ordinarily rely upon frozen-section diagnosis in these cases, although we often make frozen-sections and study them, for we feel that the differential diagnosis of these soft-part sarcomas is so difficult that permanent sections are necessary in most instances.

It should be emphasized that more extensive exploratory dissection of the tumor, or excision of a larger part of or the whole tumor for biopsy, is undesirable. It may gratify the operator's curiosity about the attachments and extent of the neoplasm but it is a serious threat to the patient's life, for it is possible that metastases may be produced by surgical dissection. A very small biopsy is usually adequate for diagnostic purposes.

The diagnosis having been proved histologically, amputation should be performed promptly. It is important that it be done at a high enough level to avoid local persistence of the disease. Like certain other types of soft-part sarcomas those developing from synovia have a tendency to extend longitudinally between fascial planes a surprising distance in the affected limb. In order to be certain of getting proximal to them amputation should be done at a high level. This means, for synovial sarcoma of the knee for instance, amputation through the upper third of the thigh, and for a lesion of the elbow, amputation through the upper third of the arm.

A final question in the treatment of synovial sarcoma concerns the regional lymph nodes. We have seen no reports of dissection of the regional nodes. Yet there have been seven instances of metastases to inguinal nodes and four cases in which the axillary nodes were involved among those which we have tabulated. Possibly, more complete follow-up data would reveal an even higher incidence of lymph node metastasis. In this respect, synovial sarcoma differs from fibrosarcoma, for the latter metastasizes to lymph nodes so rarely that the phenomenon has no significance in planning treatment. Since regional lymph node dissection is not a hazardous operation it should be seriously considered as a separate and final stage in the treatment of synovial sarcoma.

SUMMARY AND CONCLUSIONS

The synovial sarcoma is a rare, highly specialized form of malignant neoplasm which develops in the extremities. It is always composed of two sharply

contrasted tissue forms, one reproducing caricatures of synovial structures; the other resembling fibrosarcoma, and the two are inextricably intermingled. The tumor generally develops slowly, is more commonly found in young adult males, and finally metastasizes usually through the blood stream and occasionally to the regional lymph nodes. Nine new examples are summarized and are analyzed together with 95 previously reported cases. Of this group of 104, only three are known to be free from evidence of persistence or metastasis more than five years after treatment. This study leads to the conclusion that diagnosis should be established by histologic examination of a small fragment obtained by incisional biopsy which causes the least possible trauma. Treatment should be radical—high amputation and possibly regional node dissection. Radiotherapy has been little used and there is no proof that it is effective.

BIBLIOGRAPHY

Adair, F. E.: Discussion of Malignant Tumor of Synovial Membrane of Knee Joint. By Dr. W. B. Coley. ANNALS OF SURGERY, **101**, 809, 1935.

Aitkin, A. P.: Roentgenographic Recognition of Synovioma. Jour. Bone and Joint Surg., **23**, 950, 1941.

Berger, L.: Synovial Sarcomas in Serous Bursae and Tendon Sheaths. Am. Jour. Cancer, **34**, 501, 1938.

Black, W. C.: Synovioma of Hand. Am. Jour. Cancer, **28**, 481, 1936.

Bonne, C., and Collet, A. M.: Synoviomen. Geneesk. Tijdschr. v. Nederl.-Indië, **75**, 1384, 1935.

Briggs, C. D.: Malignant Tumors of Synovial Origin. ANNALS OF SURGERY, **115**, 413, 1942.

Cabot Case 24321: Synovioma of the Knee. New Eng. Jour. Med., **219**, 204, 1938.

Cabot Case 25312: Synovioma of the Knee. New Eng. Jour. Med., **221**, 196, 1939.

Chenot and Tzanck: Endothéliome synovial du pied. Bull. et mém. Soc. anat. de Paris, **87**, 293, 1912.

Coley, B. L., and Pierson, J. C.: Synovioma: Report of Fifteen Cases, with Review of the Literature. Surgery, **1**, 113, 1937.

De Santo, D. A., Tennant, R., and Rosahn, P. D.: Synovial Sarcomas in Joints, Bursae, and Tendon Sheaths: Clinical and Pathologic Study of Sixteen Cases. Surg., Gynec. and Obst., **72**, 951, 1941.

Diez, J.: El endotelioma sinovial articular. Prensa méd. argent., **18**, 487, 1931.

Eveleth, M. S., and Brezina, P. S.: Synovioma Involving the Knee Joint. Yale Jour. Biol. & Med., **16**, 27, 1943.

Faccini, U.: Un caso di peritelioma sarcomatoso della capsula articolare del ginocchio destro. Arch. ital. di chir., **7**, 481, 1923.

Fehr, A.: Zur Klinik und Pathologie der Synoviome. Beitr. z. klin. Chir., **165**, 88, 1937.

Fievez: Endothéliome de l'articulation du cou-de-pied. Bull. et mém. Soc. nat. de chir., **61**, 1034, 1935.

Fisher, H. R.: Synovial Sarcomesothelioma (Sarcoendothelioma). Am. Jour. Path., **18**, 529, 1942.

Hannemüller: Über primäre Sarkome der Gelenkkapsel. Beitr. klin. Chir., **63**, 307, 1909.

Hodgson, F. G., and Bishop, E. L.: Malignant Synovioma of Knee Joint. Jour. Bone & Joint Surg., **17**, 184, 1935.

Hohenthal, T.: Ett fall av primart knaledkapsel sarkom. Finnska Läk. Sällsk. Hand., **76**, 458, 1934.

Hutchison, C. W., and Kling, D. H.: Malignant Synovioma. Am. Jour. Cancer, **40**, 78, 1940.

Jaffe, H. L., and Lichtenstein, L.: Sarcoma (Synovioma). Bull. Hosp. Joint. Dis., **2**, 3, 1941.

Klages, F.: Endotheliosarcoma of Hip Joint. Arch. f. klin. Chir., **197**, 137, 1939.

Knox, L. C.: Synovial Sarcoma. Am. Jour. Cancer, **28**, 461, 1936.

Lazarus, J. A., and Marks, M. S.: Synovial Sarcoma: Report of Two Cases. Surgery, **13**, 290, 1943.

Lejars, and Rubens-Duval: Les sarcomes primitifs des synoviales articulaires. Rev. de chir. Paris, **41**, 751, 1910.

Leichner, W., and Schaefer, A.: Synovial Sarcoma. Conn. State Med. Jour. **5**, 113, 1941.

Lewis, R. W.: Roentgen Recognition of Synovioma. Am. Jour. Roentgenol. & Rad. Ther., **44**, 170, 1940.

Marsh, H.: Primary Sarcoma of the Knee Joint. Lancet, **2**, 1330, 1898.

Murray, M. R., Stout, A. P., and Pogogeff, I. A.: Synovial Sarcoma and Normal Synovial Tissue Cultivated *in vitro*. ANNALS OF SURGERY, **120**, 843, December, 1944.

Prym, P.: Synoviales Sarkoendotheliom des Kniegelenks. Virchow's Arch., **279**, 71, 1930.

Smith, L. W.: Synoviomata. Am. Jour. Path., **3**, 355, 1927.

Sabrazès, J., and de Grailly, R.: Les tumeurs articulaires et paraarticulaires. Synovialomes kystiques bénins (kystes séreux-synoviaus) et synovialomes malins. Gaz. hebd. d. sc. méd. de Bordeaux, **53**, 449, 1932.

Schie, E.: A Case of Synovioma in the Region of the Hip Joint. Nord. med., **7**, 1538, 1940.

Silfverskiold, N.: Few Operated Cases of Malignant Synovial Tumors; Synovialoma, Synovial Fibrosarcoma. Nord. med., **8**, 1910, 1940.

Snyder, C. H.: Malignant Synovioma of the Knee Joint. Am. Jour. Surg., **55**, 67, 1942.

Stanford, S., and Horne, E. A.: Malignant Synovioma. Jour. Bone and Joint Surg., **25**, 883, 1943.

Tavernier: Sarcome de la synoviale du genou. Lyon chir., **27**, 522, 1930.

von Verebély, T.: Beiträge zur Pathohistologie der synovialen Erkrankungen. Schweiz. méd. Schnschr., **68**, 458, 1938.

Votta, E. A.: Primary Sarcomas: Report of Case. Bol. y trab. Acad. Argent. de cir., **26**, 554, 1942.

Wagner, L. C.: Intra-articular Endothelial Tumors. ANNALS OF SURGERY, **92**, 421, 1930; *idem:* Discussion of Malignant Tumor of Synovial Membrane of Knee Joint. By Dr. W. B. Coley. ANNALS OF SURGERY, **101**, 809, 1935.

Wegelin, C.: Pathologischanatomische Demonstration (Fall 6). Schweiz. med. Wchnschr., **9**, 722, 1928.

Zwahlen, T.: Sur les synoviomes des gaines tendineuses et des bourses séreuses. Bull. Assoc. franç. p. l'étude du cancer, **24**, 682, 1935.

SYNOVIAL SARCOMA AND NORMAL SYNOVIAL TISSUE CULTIVATED *IN VITRO*

M. R. Murray, Ph.D., Arthur Purdy Stout, M.D.,
AND
I. A. Pogogeff, B.A.
New York, N. Y.

FROM THE SURGICAL PATHOLOGY LABORATORY OF THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, AND THE DEPARTMENT OF SURGERY, PRESBYTERIAN HOSPITAL, NEW YORK, N. Y.

As an adjunct to clinical and pathologic studies on synovial sarcoma conducted in this laboratory, an attempt has been made to evaluate the cultural characteristics of this neoplasm *in vitro*, and to compare it with normal synovial tissue cultivated under similar conditions.

SYNOVIAL SARCOMA

Method.—Tissue from three of the tumors described by Haagensen and Stout (Cases 3, 4 and 6) was explanted in lying-drops on cover slips according to the Maximow method. The medium used for cultivation consisted of chicken plasma (sometimes diluted with human plasma) human placental serum, extract of 9–11-day chicken embryos or of adult rat spleen in buffered saline, and serum ultrafiltrate (Simms and Sanders, 1942).

The cultures were washed in the buffered saline three times a week, at which time the liquid components of the medium were renewed. The explants were maintained in their original situation on the flying coverslip as long as possible, in order that the organization and pattern of the outgrowth, as well as its products, might be most advantageously studied. But the fibrinolytic activity of the tumor cells made transferal necessary after one or two weeks. An admixture of human plasma in the clot hastened liquefaction.

Explants from Case 3 were cultivated up to 28 days; from Case 4 up to 36 days; and from Case 6 up to 53 days. During this time they were fixed, at intervals, in 10 per cent formalin, in 2 per cent $AgNO_3$ or in Zenker's, Helly's or Bouin's fluid. They were stained with Delafield's hematoxylin, Mallory's phosphotungstic acid hematoxylin, Weigert's hematoxylin with mucicarmine, toluidine blue, fuchsin-ponceau-aniline blue, or impregnated with silver by McKinney's modification of the Bielschowsky method for reticulin.

Growth Characteristics.—When cultivated *in vitro*, each of these three tumors produced, in varying proportions, two main types of outgrowth—a flat, shelf-like, membranous or epithelioid form; and a tissue composed of rather flattened spindle-shaped cells.

The cells which adopted the membranous habit were broad and flat, often fan-shaped or spidery (Figs. 1 and 4) with the ectoplasmic region greatly attenuated. When a culture was impregnated with $AgNO_3$ these cells were shown sometimes to be contiguous, forming a true membrane with a mosaic of black cell borders (Fig. 8) and sometimes to exist discretely, only over-

FIG. 1 FIG. 2

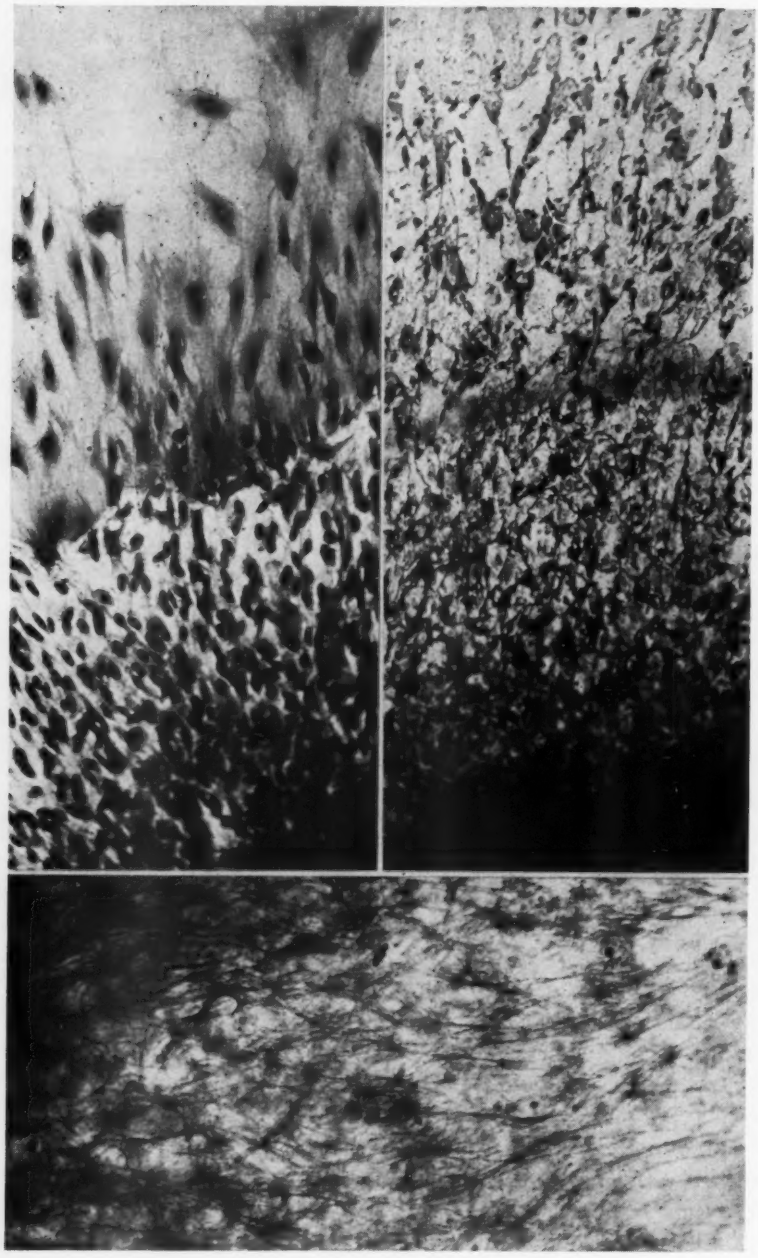


FIG. 3

FIG. 1.—Case 4: Synovial sarcoma. 28 days *in vitro*. Fixed in Zenker's fluid, stained with Harris' hematoxylin. Shows spidery type of synovial cell beyond the liquefaction line.

FIG. 2.—Case 4: Synovial sarcoma. 12 days *in vitro*. Impregnated with silver nitrate to show cell boundaries.

FIG. 3.—Case 4: Synovial sarcoma. 19 days *in vitro*. Stained by McKinney's modification of Bielschowsky, demonstrating recticulin formation.

lapping here and there (Fig. 2). They are rather small compared to epithelial cells, and have large oval nuclei with a variable number of chromatin nucleoli (from two to seven) a scattering which we have found characteristic of mesoblastic cells *in vitro*. Division is frequent and is by mitosis. The nuclear and nucleolar picture is the same in the spindle-shaped cells of the second type of outgrowth. Though they are more often discrete (Fig. 9), they may lie parallel and close together forming a sheet, as in Figure 5. The two types of outgrowth, though often distinct, may overlap in the same culture. It seems probable that they represent merely two developmental potentialities of the same cell, a cell with capacities rather similar to those of the serosal cell.

These tumor cells show a fairly strong fibrinolytic activity, and in a liquefied area of a culture, the edge of the explant is often "healed over" by cells which creep along the surface and extend themselves over it. There is a tendency for necrotic patches to develop in the growth and in the explant. These appear at the edges as well as in the central portions of the culture, seemingly without reference to the thickness of the area in which they occur. We have often observed this in cultures of tumors which are characterized by spontaneous necrosis. It seems, also, to occur in the normal joint capsule, though probably as a result of trauma (*cf.* Efskind, 1941), and in the normal serosa as a response to injury (Maximow, 1925). It is not uncommon to find migrant or "metastatic" nodules at varying distances from the explant. Sometimes these are seen still connected with the explant by one or two cells pulled thin in the form of a stalk.

Reticulin is formed *in vitro* around cells of both types—membranous and spindle-shaped. In the former the fibers are exceptionally fine (Fig. 3). Conceivably, this fineness may account for the fact that they are not observed between the cuboidal and columnar cells which enter into epithelial formations in the sections of the tumor. Reticulin formation in these cultures is rather slow as compared to that by normal fibroblasts.

Both early and late in the course of cultivation, and in both types of cells, moderately refractive vacuoles may appear (Fig. 9). These become lavender when Nile blue sulfate is applied supravitally. They do not stain with mucicarmine or with toluidine blue. Sometimes small cavities lined with cuboidal cells are formed near the border of the explant, containing a fluid similar to the lavender vacuoles.

The presence of many wandering cells characterized these cultures. These generally fell into the classifications of lymphocytes and macrophages. The latter were still present in fair numbers after 24 days *in vitro*. They often contained material which stained red with mucicarmine, though the tumor cells present in the same cultures did not.

As the culture period advanced, cells which could not be distinguished from fibroblasts appeared, and in some cultures came to form the major part of the outgrowth. The origin of these cells is obscure. It cannot be said with certainty whether they represent a further modification of the second type of tumor cell, or whether they are the descendants of cells originally

FIG. 4

FIG. 5

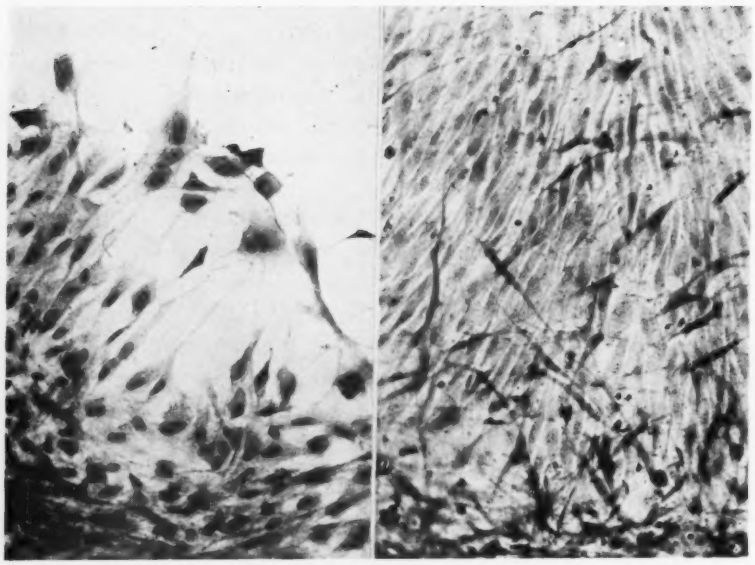


FIG. 6

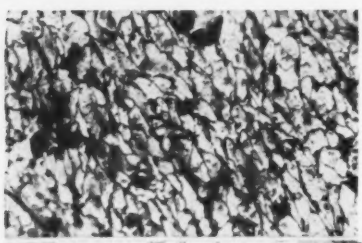


FIG. 7

FIG. 8

FIG. 9

FIG. 4.—Case 4: Synovial sarcoma. 28 days *in vitro*. Epithelioid and spidery type of outgrowth. Fixed in Zenker's fluid, stained with Harris' hematoxylin.

FIG. 5.—Case 6: Synovial sarcoma. 10 days *in vitro*. Flat spindle cell type of outgrowth; note wandering cells. Fixed in Bouin's fluid, stained with acid fuchsin, ponceau, aniline blue.

FIG. 6.—Synovial cells from knee joint of normal adult rat. 15 days *in vitro*. Impregnated with silver nitrate to show cell borders.

FIG. 7.—Spidery type of synovial cell from knee joint of normal adult rat. 24 days *in vitro*. Bouin's fluid, acid fuchsin, ponceau.

FIG. 8.—Case 3: Synovial sarcoma. 18 days *in vitro*. Impregnated with silver nitrate to show cell boundaries.

FIG. 9.—Case 6: Synovial sarcoma. 8 days *in vitro*. Spindle cells containing vacuoles which do not stain with mucicarmine. Zenker's fixative, Weigert's hematoxylin, mucicarmine.

present in the invaded tissue or associated with the blood supply of the tumor. In Case 6, however, where there was a good deal of granulation tissue present in the portion of the tumor obtained for study, the later growth of fibroblasts was greatest. In Case 4, fibroblasts did not appear in the outgrowth except in one slide: the cells were almost entirely of the first, or membrane-forming type. Yet the portion of the tumor adjacent to that from which the explants were made contained almost entirely the interlacing spindle-shaped type of cell, in histologic preparations.

NORMAL SYNOVIAL TISSUE FROM KNEE JOINT OF ADULT RAT

The normal tissue was grown by the same method as the tumors. The medium also was the same as used in the neoplastic cultures except for the addition of rat plasma or rat serum.

The growth from the synovial lining of the adult rat knee joint, the patellar and fat pad regions, is of a specific nature. The synovial cell proper appears to be a relatively small one, capable of assuming diverse and transitional forms varying from spindle to spidery to epithelioid. It has a distinct round nucleus which may at times be elongate, depending on the form of cell, with one to four nucleoli (occasionally a cell with five or six is seen). The cytoplasm is somewhat finely granular, although in the early days of culture, large refractive granules can be seen and are rather abundant in cultures where the explant contains fat. As the culture grows older vacuoles may appear within the cytoplasm.

The growth pattern is one of membranes, chains, and wandering cells. The cells of the membrane can be spindle-shaped, spidery or epithelioid, with transitional forms of each (Figs. 10, 7 and 11). The spindle-shaped cells may at times be somewhat like fibroblasts. Among the spidery types one may see cells which have a long basal process. The chains, likewise, may be composed of spindle-shaped cells or rounded ones which may have processes. The chains of rounded cells present a bead-like appearance. These chains may branch sidewise, and may broaden by multiplication to produce little islands of tissue along their length (Fig. 12). Some of the cells are able to migrate well into the region beyond the general outgrowth. The wandering cells behave rather like macrophages, existing in rounded-up or spread-out forms.

Mitosis is found among the cells of the membranes and chains and probably also may take place among the wandering cells. Amitosis probably occurs. Occasional flattened cells are seen which have two to four nuclei. The cells produce a moderate amount of liquefaction. The fibrinolysis is slow compared to that of epithelial growths.

Lithium carmine, added to the washing saline, showed that some of the cells were capable of phagocytic function; the dye particles being taken up not only by the wandering macrophage-like forms but also as fine granules by epithelioid, spindle and spidery types.

On the basis of this, and, also, because one can see cells which seem to be

FIG. 10

FIG. 11

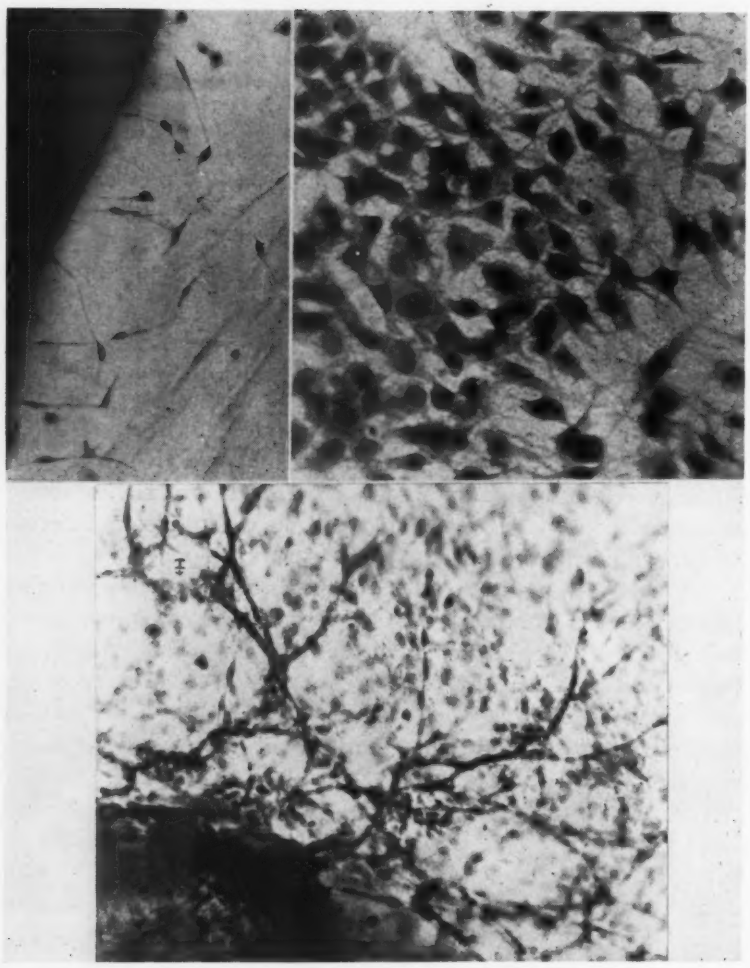


FIG. 12

SYNOVIAL CELL FROM KNEE JOINT OF ADULT RAT

FIG. 10.—Spindle cells-outgrowth at 5 days. Helly's fluid, Harris' hematoxylin.

FIG. 11.—Portion of a membranous outgrowth, showing intermediate epithelial and spidery forms. 13 days *in vitro*. Zenker's fluid, Harris' hematoxylin.

FIG. 12.—Growth in chains with island formation "I". Background of epithelioid cells. 15 days *in vitro*. Zenker's fluid, Harris' hematoxylin.

transitional, *i.e.*, have a typical synovial nucleus and yet appear ameboid, one is led to believe that the synovial cells can assume a macrophage-like form.

Supravital staining with neutral red showed granules which were reddened by this dye in all the cell types. In the macrophage-like cells the staining was brilliant. In the other cells the granules were rather fine and usually clumped to one side of the nucleus, but at times were arranged perinuclearly as well. As the age of the culture increased, these granules seemed to become more numerous in the cells. Some of the later appearing vacuoles also were stained by this dye.

Nile blue sulfate also was used supravitally, and showed bright blue granules of varying size, generally rather large and few in number, scattered throughout the cytoplasm in all the cells.

The cultures were fixed and stained routinely as described for the tumor preparations. Staining with $AgNO_3$ revealed borders similar to those found in the tumor cultures (Fig. 6). The McKinney modification of the Bielschowsky method used as in tumor cultures failed to demonstrate reticulin. The use of mucicarmine stain gave negative results.

Discussion.—Since this paper and the foregoing one (Haagensen and Stout) are concerned primarily with the synovial sarcoma in various of its aspects as a neoplasm, it does not seem suitable to discuss at length here the disputed problem of the nature and relationships of the normal synovial cell. For this the reader may be referred to Petersen's contribution on the joints, in von Möllendorff's Handbuch der mikroskopschen Anatomie des Menschen, 1930 (Die Gewebe II, pp. 648–680), and to a more recent summary by L. Efskind (1941).

Judging from the histologic sections of these tumors, we are dealing with a neoplasm in which two morphologically distinct cell types coexist and display cancerous properties. This condition is most nearly paralleled by the mesothelioma, in which, also, two elements, of epithelial and fibrous habit, are the rule (Stout and Murray, 1942).

In the tissue cultures of the synovial sarcomas two cell types and growth habits prevail, though the distinction between these is much less sharp than it appears *in vivo*. From observation of the cultures, one is inclined to conclude that the distinction is not a generic one but that the same cell may potentially assume either form. Bearing on this point is the discrepancy between the sections of the tumor in Case 4, and its outgrowth *in vitro*: the sections showed mainly fibrous tissue, and the cultures almost entirely an epithelioid type of outgrowth. This same situation was encountered in a mesothelioma previously studied (Stout and Murray, 1942), in which the sections were entirely fibrous (resembling a fibrosarcoma) and the outgrowth entirely membranous.

The cultures of normal rat synovium showed the synovial cells to be capable of considerable polymorphism. In general, the human tumor cultures parallel those from the normal rat knee joint as regards form and behavior, though in the latter more diversity of form and more extremely distinctive

cell types are encountered. The characteristic "spidery" form of the synovial cell is frequently reproduced by the tumor cultures. Our normal study confirms the view of Vaubel (1933), that the synovial cell is a specific type of cell, distinct from the fibroblast; and our cultures from the rat's knee reproduce to a considerable degree the forms depicted by him from cultures of synovial cells from the fat-pad of the rabbit's knee. Vaubel regards the synovial cell as most nearly resembling the serosal cell, though being distinct from it. In our study, this appears to be a particularly apt comparison where the tumors arising from these two tissues are concerned.

The fibrosarcomatous component of the synovioma is difficult to reconcile with a view such as Efskind's (1941), derived from the study of stretch preparations of normal and regenerating synovial membranes of the rabbit's knee. He states that the cells of the synovial membrane have no capacity for the formation of fibroblasts, and there are no fibers found among synovial cells. We are inclined to believe that such cells as we see in our cultures exhibiting the typical characteristics of fibroblasts are not synovial cells, but have some other origin. Yet, in the tumor cultures, the membranous type of synovial cell can certainly form reticulin fibers; and the nonepithelial portions of the tumor sections are richly supplied with reticulin. One is reminded of the work of Maximow (1927), and of Schopper (1932), on the serous membranes. Normal mesothelial cells did not form connective tissue *in vitro;* but under conditions of inflammation, and of irritation of the peritoneum by *kieselguhr,* these cells took on the form and characteristics of typical fibroblasts. It may be that in the neoplasm some comparable physiologic state exists.

The continued presence of wandering cells in the tumor cultures after as much as a month *in vitro* is of interest, especially since the normal synovial cells *in vitro* may assume a macrophage-like form. It has been noted that we were not able to produced positive results *in vitro* with the mucicarmine stain except in the wandering cells of the tumor cultures. Nor did we obtain metachromatic staining with toluidine blue. The significance of these negative findings is doubtful, since the technics (especially that of metachromatic staining) are capricious *in vitro* (*cf.* Davies, 1943).

SUMMARY AND CONCLUSIONS

1. Material from three human synovial sarcomas has been cultivated *in vitro,* and its characteristics compared with similarly treated normal synovial tissue from the knee joint of the adult rat.

2. In general, the human tumor cultures parallel those from the normal rat knee joint as regards form and behavior, though the normal cultures exhibit more diversity of form and more distinctive cell types.

3. The normal synovial cell appears to be a specific cell type distinct from other epithelium and from the fibroblast.

4. The synovial sarcoma appears to be a distinct type of neoplasm exhibiting certain similarities to the mesothelioma.

BIBLIOGRAPHY

Davies, D. V.: The Staining Reactions of Normal Synovial Membrane: With Special Reference to the Origin of Synovial Mucin. J. Anat., **77**, 160–168, 1943.

Efskind, L.: Experimentelle Untersuchungen über die Anatomie und Physiologie der Gelenk Kapsel. I. Die normale und pathologische Histologie der Synovial membrane. Acta Orthopaedica Scandinavica, **12**, 214–266, 1941.

McKinney, R. L.: Studies on Fibers in Tissue-Culture. III—The Development of Reticulum Into Collagenous Fibers in Cultures of Adult Rabbit Lymph Node. Arch. f. exper. Zellforsch., **9**, 14, 1929.

Maximow, A.: Über das Mesothel (Deckzellen der serösen Haute) und die Zellen der serösen Exsudate: Untersuchungen an entzündetem Gewebe und Gewelbskulturen. Arch. f. exper. Zellforsch., **4**, 1, 1927.

Petersen, H.: Die Gelenke, page 648–680 in W. von Mëllendorff: Handbuch der mikroskopischen Anatomie des Menschen. Die Gewebe II, 1930.

Schopper, W.: Explantations studien an Blutgefässen und Serösen Hauten. Beitr. z. path. Anat. u. z. allg. Path., **88**, 451–537, 1932.

Simms, H. S., and Sanders, M.: Use of Serum Ultrafiltrate in Tissue Cultures for Studying Deposition of Fat and for Propagation of Viruses. Arch. Path., **33**, 619–635, 1942.

Stout, A. P., and Murray, M. R.: Localized Pleural Mesothelioma: Investigation of Its Characteristics and Histogenesis by the Method of Tissue Culture. Arch. Path., **34**, 951–964, 1942.

Vaubel, Ernst: Über das Synovial gewebe. Virchow's Arch. path. Anat., **289**, 671, 1933.

Vaubel, Ernst: The Form and Function of Synovial Cells in Tissue Cultures. I Morphology of the Cells Under Varying Conditions. J. Exp. Med., **58**, 63, 1933.

Vaubel, Ernst: The Form and Function of Synovial Cells in Tissue Cultures. II The Production of Mucin. J. Exp. Med., **58**, 85, 1933.

PHYSIOLOGIC OBSERVATIONS ON PATIENTS WITH EXTERNAL PANCREATIC FISTULA

CAPT. JOSEPH M. MILLER, M.C.,
AND
MAJ. THOMAS B. WIPER, M.C.
ARMY OF THE UNITED STATES

WITH THE TECHNICAL ASSISTANCE OF G. MARGARET ROURKE, B.S., ELEANOR FOGERTY, A.B., AND JANE LA FETRA, B.S.

DURING THE PAST TEN YEARS, there have been only rare reports appearing in the medical literature of physiologic observations made upon human subjects with external pancreatic fistula.[5, 6, 7, 8, 14, 18, 19, 20, 21, 23] The fundamental information concerning pancreatic function has been derived from the experimental laboratory animal, whereby, with painstaking care, the fundamentals of pancreatic secretion have been investigated.[1, 2, 9, 12, 22] Rarely has the clinician been given the opportunity to correlate the physiologic observations made upon the human with the results obtained from the experimental animal. The recent advances made in the operative attack upon lesions of the pancreas make it imperative that the surgeon be more conversant with the physiology of that organ, for interference with the normal flow of the external secretion will result in profound alterations in total metabolism.

Except for occasional instances, studies made on the human of pancreatic flow and the various constituents of the external secretion have of necessity been done by intubation of the duodenum. Therefore, it was a privilege to have at our disposal three individuals each of whom had an external pancreatic fistula.

This offered us a rare opportunity to make observations on the influence of such persistent fistulae upon the patients, particularly with reference to the many alterations induced:

1. General nutritional state of the patient.
2. Total pancreatic flow in 24 hours.
3. Pattern of flow in 24-hour period.
4. Plasma electrolyte pattern.
5. Plasma protein.
6. Influence of water intake on pancreatic flow.
7. Observations on volume flow alterations induced by the administration of various substances into the duodenum.
8. The effect of intravenous fluids upon pancreatic secretion.
9. Observations on volume flow alterations induced by the administrations of drugs subcutaneously.

These observations, as reported in the statistical study presented in this paper, are concerned with the most productive of these fistulae, but our conclusions are drawn from a survey of the three patients, all of whom reacted similarly.

It is well at this time to present the normal values of the individual constituents of pancreatic juice. We consider these normal values, as they were derived from a study of the three individuals previously mentioned who were in widely different states of metabolic balance as far as clinical and laboratory observations were concerned. However, careful analysis of their pancreatic secretions revealed little dissimilarity in composition, and correlated with the isolated reports of the structure of pancreatic secretion appearing in the literature. We feel that these observations and facts are of value, particularly to the surgeon, as they are based upon the study of human secretions, and that emphasis should be put upon their study by the reader, as they have been but rarely called to attention in the past (Table I). Similar studies have been conducted by Krogut, Matzner and Sobel.[14]

TABLE I

ANALYSIS OF PANCREATIC FLUID

Sodium	138 mEq./L.
Calcium	2.2–3.2 mEq./L.
Chloride	60–80 mEq./L.
Bicarbonate	60–75 mEq./L.
Total protein	190–340 mg. per cent
Albumin	60 mg. per cent
Globulin	40 mg. per cent
Nonprotein nitrogen	14.3 mg. per cent
Urea nitrogen	5 mg. per cent
Uric acid	0.2 mg. per cent
Nucleoproteins, Proteose, Cholesterol, Sugar, Sulphates	Not present

The physical characteristics of pancreatic secretion in the human have been previously recorded. It is a clear, opalescent fluid, alkaline in reaction, with a p_H ranging from 7.5 to 8.0. In addition to the various salts, three chief enzymes are present. These are lipase, amylase and trypsinogen. The secretion of pancreatic juice is known to be under both hormonal and nervous control. The chief effect of secretin is to cause the production of water and inorganic salts. Vagal stimulation results in the secretion of pancreatic juice, but the amount is much less than that produced by secretin. The vagal secretion is thick, scanty, and rich in ferments. The two stimulants are normally effective simultaneously, and the ferments are washed from the alveoli by the tide of alkaline secretin juice.

A brief résumé of the experiences of the three patients is presented to allow the reader an introduction to the type of material used in this study.

Case 1.—Age 24, developed a pancreatic cyst subsequent to abdominal injury in an automobile accident. Marsupialization of the cyst was accomplished surgically, and a fistula resulted, producing 500 cc. of pancreatic secretion in 24 hours.

Flow of pancreatic juice was irregular in quantity and gradually decreased until spontaneous closure occurred about two months after submission to our care.

No significant changes in blood chemistry were found during the latter part of his hospital course except an elevation of plasma chlorides to an approximately normal value of 101.2 mEq. per liter.

Case 2.—Age 26. This individual had four episodes of abdominal cramps, nausea and vomiting. A diagnosis of some acute intra-abdominal pathology was made and an incision and drainage of an abscess involving the pancreas and lesser sac was done. Drainage of pancreatic fluid of approximately 100 cc. was noted shortly after operation and persisted until admission to our care.

Table III presents an essentially normal pattern. The details of the closure of this fistula are reported elsewhere.

Case 3.—Age 25. This patient sustained a gunshot wound of the upper abdomen, one of the sequelae of which was an external pancreatic fistula. This persisted in spite of attempted surgical repair elsewhere, and at the time of admission to our care was productive of large quantities of pancreatic fluid.

Table IV is a presentation of the marked changes in blood constituents found in this individual. The apparently normal values of some of these constituents will be shown to be misrepresentations, as will be explained subsequently.

TABLE II

BLOOD STUDY OF CASE 1 AT THE TIME OF RECEPTION IN HOSPITAL

R. B. C.	5,080,000. per cu. mm.
W. B. C.	12,300. per cu. mm.
Hb.	90.0 per cent
Hematocrit	46.8 per cent
Sed. rate	0.60 mm./min.
N. P. N.	24.8 mg. per cent
Serum protein:	6.97 gm. per cent
Serum albumin	4.50 gm. per cent
Serum globulin	2.47 gm. per cent
Chloride	96.0 mEq./L.
Carbon dioxide combining power	30.9 mEq./L.
Prothrombin time	26.0 secs.

TABLE III

BLOOD STUDY OF CASE 2 AT THE TIME OF RECEPTION IN HOSPITAL

R. B. C.	4,280,000. per cu. mm.
W. B. C.	6,200. per cu. mm.
Hb.	12.4 gm. per cent
Hematocrit	38.8 per cent
Sed. rate	0.6 mm./min.
N. P. N.	28.9 mg. per cent
Serum protein	6.85 gm. per cent
Sodium	140.6 mEq./L.
Chloride	103.0 mEq./L.
Carbon dioxide combining power	31.2 mEq./L.

TABLE IV

BLOOD STUDY OF CASE 3 AT THE TIME OF RECEPTION IN HOSPITAL

R. B. C.	5,080,000. per cu. mm.
W. B. C.	12,200. per cu. mm.
Hematocrit	44 per cent
Sed. rate	1.88 mm./min.
N. P. N.	40.0 mg. per cent
Serum protein:	7.96 gm. per cent
Serum albumin	4.92 gm. per cent
Serum globulin	3.04 gm. per cent
Sodium	113.3 mEq./L.
Chloride	91.2 mEq./L.
Carbon dioxide combining power	16.3 mEq./L.

GENERAL NUTRITIONAL STATE OF THE PATIENT

The general nutritional state of these individuals is directly proportional to the severity of the fistula. The first patient had experienced rather marked weight loss which at the time he came under our care he had partially regained. Gradual diminution in flow of the fistula was accompanied by increased appetite and gradual increase in weight. By the time closure of the fistula occurred, normal weight had been restored.

This parallelism in weight and pancreatic secretion loss is demonstrated in the fact that the second of these individuals, who was losing the least amount of secretion, presented the least alteration of body substance.

The loss of large amounts of pancreatic secretion in the third individual produced a profound alteration in physical appearance, with marked reduction in weight, and was associated with a symptom complex not unlike that demonstrated in Addison's disease.

Inasmuch, as the metabolic and physiologic changes evidenced in the first two patients were minimal, we will confine ourselves to reports concerning the reactions of Case 3.

TOTAL PANCREATIC FLOW IN 24 HOURS

The total quantity of pancreatic juice excreted in 24 hours was the first problem to attract our attention. Estimates of other investigators have placed the daily amount of pancreatic flow into the duodenum in a range varying from 500 to 1500 cc., with the usual figure for man being accepted as 700 cc. In 27 investigations of external pancreatic fistula reviewed by McCaughan, Sinner and Sullivan,[20] the least amount of pancreatic juice secreted from an external fistula was 30–40 cc. per day and the largest 1384 cc. Our individual produced through an external fistula amounts ranging as great as 1770 cc. per day. It should be stated that intestinal digestion in this patient was not disturbed, and that stools were normal in appearance and fat content. Therefore, the fistula was not total in nature, and the justifiable assumption was made that enough pancreatic secretion to provide for intestinal needs was being delivered into the duodenum. This might bring the total quantity of daily secretion to 2400 cc. a day, or perhaps more, if the usual accepted quantity of 700 cc. necessary for digestion is added to the amount lost externally by this individual. This last figure, which is about four times the value previously accepted as normal for total volume secretion in 24 hours, is great enough that the physiologic aspects of pancreatic secretory volume must be reevaluated.

PATTERN OF FLOW OF PANCREATIC SECRETION IN 24-HOUR PERIOD

Chart 1 does not represent the consolidated pattern of flow of pancreatic secretion for all of the days the patient was under observation but is a representative day in which the patient was on a high caloric diet, ingesting supplemental liquids as his appetite dictated without supervision or suggestion on the part of the hospital staff.

It will be observed from studying Chart 1 that the volume flow during the daytime was greater than night, and postprandial secretion showed a decided increase.

Fever has been reported as being a cause of diminution of flow. It was our observation that fever in itself was not the cause of diminution of flow but a symptomatic manifestation of obstruction of the fistula. This phenomenon was repeatedly seen.

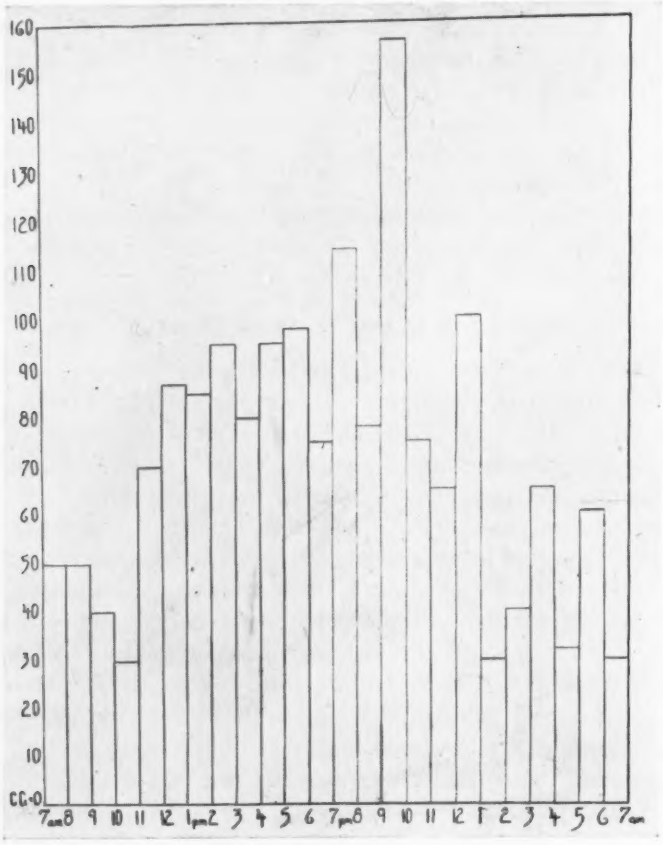


CHART 1.—Case 3: Pattern of flow of pancreatic secretion in 24 hours.

PLASMA ELECTROLYTE PATTERN

The results of severe continued loss of pancreatic fluid containing large amounts of electrolytes produce changes in plasma electrolyte pattern, as presented in Chart 2.

Sodium

The marked loss of sodium ion from the body through the external pancreatic fistula had lowered the concentration of this ion in the blood plasma from a normal of 142 mEq./L. to 113.3 mEq./L.

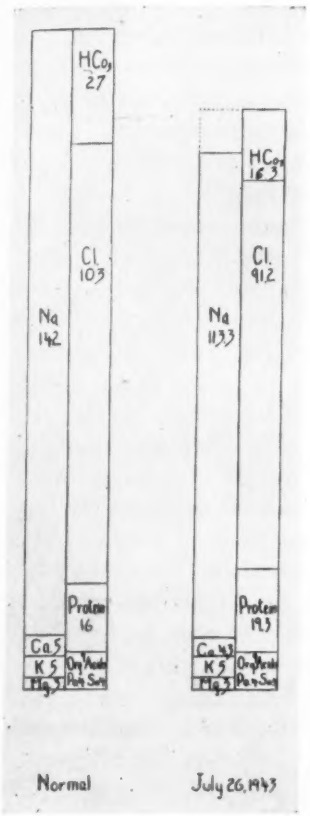


CHART 2.—Case 3: Blood electrolytes of Case 3 compared to normal. (The normal is taken from the work of Gamble[10])

The values for K., Mg. and organic acids in our chart are assumed.

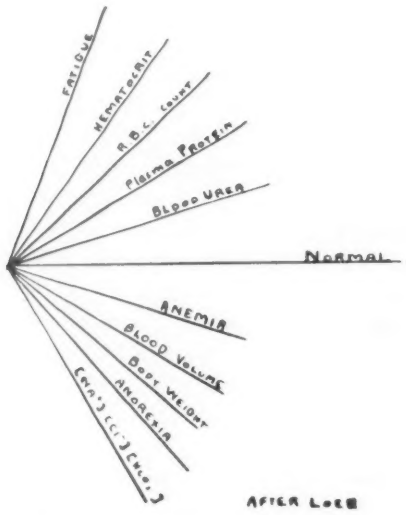


FIG. 1.—Manifestations of sodium ion loss.

A careful study of the observations made upon our patient has led us directly into the consideration of the symptom complex associated with the reduction of the sodium ion in the circulating blood plasma. These symptoms, as manifested by our patient are: Lethargy; mental torpitude; anorexia; nausea; fatique upon slight exertion; and marked dehydration.

A study of the allied blood findings associated with sodium deficiency in the circulating blood plasma in this individual reveals great similarity to the state manifest in experimental sodium chloride deprivation in the human, Addison's disease, and in the adrenalectomized animal.

McCance[16] produced sodium deficiency in experiments upon the human and found that the following changes in the blood occurred: There was a rise in erythrocyte count, hemoglobin, red blood cell volume and plasma protein concentration. These alterations occurred coincidental with a marked decrease in the sodium ion concentration in the blood plasma. These were interpreted to represent the manifestations of a loss of extracellular fluid. The symptomatic manifestations of this deprivation were expressed in a drop in circulating fluid, the sense of loss of taste, anorexia, nausea, fatigue and a marked sense of exhaustion, with dulling of the mental faculties.

Addison's disease is associated with a marked reduction of sodium ion in the circulating medium. This loss of sodium, and secondary loss of water, occurs through the kidneys and may be sufficient to produce profound

alterations in extracellular fluid distribution, as evidenced by low blood volume, high hemoglobin concentration and elevated serum protein values.

The importance of sodium loss in adrenalectomized animals was first pointed out by Loeb, and his associates.[15] Many of the characteristic changes in certain aspects of metabolism, circulation and blood concentration, found by these investigators, were also noted in the individual under study.

It is our feeling that the effects of the loss of sodium are fundamentally the same whether it be experimentally through the skin, through the kidneys, as the result of removal of the adrenals, or as in our patient, by loss through an external pancreatic fistula.

The fact that these effects were due to a loss of sodium in our individual was proven by a reversal of the changes enumerated above when the sodium deficiency was compltely corrected.

Calcium

We believe that we have encountered a phase of calcium metabolism which has not received the attention it deserves. It is generally recognized that calcium is absorbed in the upper intestinal tract and that it is excreted in the urine[17] and the feces.[11] It is the opinion of some observers that fecal calcium is calcium which has never been absorbed from the intestinal tract. However, it is the feeling among others that calcium is absorbed in the upper intestinal tract and later excreted through the large bowel.[3] Animals on a calcium-free diet will excrete calcium into the intestinal tract.[3] This calcium comes from the extracellular fluid and has previously been liberated from bone, as indicated by osteoporosis.

We have, as have other investigators,[14] found that calcium is excreted in pancreatic juice draining from an external fistula. At one time 2.2 mg. per cent and another 3.24 mg. per cent were found in the pancreatic secretion. Ordinarily this would be discharged into the duodenum. This fact would indicate that a cycle of calcium conservation is present in which the ionizable calcium in the extracellular fluid is discharged into the upper intestinal tract in the pancreatic secretion. This, as previously indicated, is in the secretin fraction of pancreatic secretion. A fraction of the calcium discharged into the upper intestinal tract in the pancreatic secretion may be absorbed, the remainder may pass out in the feces.

This calcium exists as ionizable calcium as distinguished from calcium which is nonionizable or protein-bound. The former is free to diffuse from the blood plasma into the other extracellular fluids. The calcium content of the latter is of necessity lower than that in blood plasma as protein-bound calcium cannot pass across the cell membrane.

The total blood calcium of this individual on one occasion was 8.6 mg. per cent, and the calcium determination made on a pooled specimen of pancreatic fluid was 3.24 mg. per cent. It is generally recognized that 55 per cent of calcium in plasma is in diffusible form.[3] Evaluation of the figures obtained of the observations in this individual reveals that a process of filtration may

be occurring, inasmuch as the value of 3.24 mg. per cent diffusible calcium found in the pancreatic secretion approaches the calculated value of 4.73 mg. per cent of diffusible calcium for this individual.

Chloride and Bicarbonate

A marked decrease in plasma chloride had occurred, as evidenced in Chart 2, with a fall from 103 mEq./L. to 91.2 mEq./L. as a result of the continued loss of 60–70 mEq./L. in the pancreatic secretion. This loss of chloride did not directly parallel the loss of sodium because of the large amounts of bicarbonate lost in pancreatic secretion.

Pancreatic secretion has an alkaline p_H ranging from 7.5 to 8. This is thought to be due to the high concentration of bicarbonate found in the secretion, the figure for bicarbonate being 60–90 mEq./L. whereas, in the blood it exists in a normal concentration of approximately 27 mEq./L. Our patient, however, had a blood concentration of bicarbonate of 16.3 mEq./L.

This is a manifestation of the continued drain on tissue reserves of chloride and bicarbonate which were being continually lost from the body by the disturbed mechanism of chloride and bicarbonate conservation which normally exists through reabsorption of pancreatic secretion from the bowel.

We had expected that the appearance of chloride and bicarbonate in the pancreatic secretion would be in approximately the same ratio in which they appeared in the blood plasma. The fact that this parallelism did not exist was surprising to us. We observed that the sum of the mEq./L. of chloride and bicarbonate closely approximated that of sodium, with preservation of ionic balance across the membrane. This fact is a manifestation of the preservation and economy of chloride ion retention in the blood plasma. It has been seen that the concentration of bicarbonate in the pancreatic secretion is approximately four to five times that in which it exists in the blood plasma. An explanation of this unexpectedly high value for bicarbonate concentration in the pancreatic secretion has been presented by Komarov, Langstroth and McRae,[13] who state that the increase in bicarbonate ion concentration in pancreatic juice observed with increasing activity of the gland is due to the increased rate at which carbon dioxide is formed as a metabolic product within the gland. On this basis, a part of the bicarbonate ion has its immediate origin within the secretory cells. These observers, likewise, noted that the increase in bicarbonate ion was accompanied by a decrease in chloride ion concentration to such an extent that the sum of both in mEq./L. remained relatively constant.

The following is suggested as an explanation of this phenomenon by the above mentioned authors:[13] "A difference in net ionic charge on two sides of a membrane results in an electrical potential difference across it. This potential difference facilitates the passage into the cell of ions of one sign, but hinders that of ions of the other. An increased rate of formation of anions (HCO_3) within a cell, due to increased metabolism, results in a change in the potential difference favoring more rapid passage of cations (Na-K-Ca)

but retarding the passage of anions (Cl and HCO_3) from the blood stream or tissue fluids. Since the cations already pass easily through the membrane at the maximum rate (the concentrations in the secretion are comparable with those in the serum), the principal effect is a retarding of the passage of anions, and so appears a decrease in the Cl concentration of the secretion."

Further support to this theory is given by the observation in our series that where glandular activity increased carbon dioxide combining power of the secretion increased and chloride concentration diminished (Table V). We also observed the converse of this phenomenon (Table VI).

TABLE V

DETERMINATIONS ON PANCREATIC SECRETION FOLLOWING INTRAVENOUS ADMINISTRATION OF 5 PER CENT GLUCOSE IN PHYSIOLOGIC SALINE*

	Carbon Dioxide Combining Power	Chloride	pH
Control	54.6	78.	7.5
After 1000. cc.	80.8	51.	8.0
After 2000. cc.	80.8	51.	8.0

*The above figures are mEq./L. for pancreatic secretion.

TABLE VI

DETERMINATIONS ON PANCREATIC SECRETION FOLLOWING HYPODERMIC ADMINISTRATION OF VARIOUS DRUGS*

	Carbon Dioxide Combining Power	Chloride
Control	54.6	78
Ephedrine	57.3	67
Pilocarpine	34.9	67
Atropine	27.2	51

* All the above values are expressed in mEq./L. for pancreatic secretion showing alteration in crystalloids composition following subcutaneous injection of the indicated drugs.

PLASMA PROTEIN

The maintenance of a normal body fluid volume is dependent upon the presence of adequate amounts of fluid, electrolytes and protein. Alteration in any or all of these constituents produces profound changes.

Pancreatic fluid containing water, electrolyte and protein, was lost through the external fistula. In addition, the proteins necessary to retain fluid in the circulating blood volume were depleted from lack of protein ingestion and by the presence of infection.

With the shrinkage of effective blood volume, there is a false relative rise in the concentration of plasma protein, though the actual total amount of circulating protein is much below the calculated normal for that individual. This phenomenon has been commented upon previously by Gamble.

The initial studies of protein, hematocrit, and erythrocyte count in this individual were 7.96 Gm. per cent, 44 per cent, and 5,080,000 per cu. mm., respectively. How normal these figures appear, except for a slight elevation in protein concentration. Mere observation of the individual told one that these carefully made laboratory determinations did not present an accurate picture of the metabolic state. He was emaciated and dehydrated; his entire

action impressed one with the fact that here was an individual whose bodily stores were depleted to the breaking point, and who, in paradoxical fashion, presented a normal blood picture for these constituents. He was in vibrant health in the laboratory, but practically dead on the ward.

It is unfortunate that the means for determination of total extracellular fluid and blood volume were not at our disposal. It is in a case such as this that determinations of extracellular fluid and blood volume are of inestimable value. A correct lead would have immediately been presented from their study. Additional information can be obtained from the determination of the concentration of other blood constituents such as sodium, chloride, and bicarbonate. We feel that information concerning the concentration of the latter three constituents offer a more accurate picture of the true physiologic state in the dehydrated individual than the more usually employed procedures of protein determination, hematocrit, and erythrocyte count. Where total fluid determinations can be obtained, they should invariably be made.

With clinical improvement of the individual, it was noted that the concentration of protein, the hematocrit, and the erythrocyte count became lower. This was an expression of the fact that the circulating blood volume was gradually increasing and dilution of these elements was present. It was only when the individual was able to move into a positive phase of protein and erythrocyte production and when the blood volume had approached normal, that a true rise in concentration of these constituents was found. This phenomenon is mirrored by the fact that the concentration of the various electrolytes—sodium, chloride, and bicarbonate—rose in parallel fashion to normal level.

In the preceding paragraphs, we have recorded the physical appearance of this individual upon reception at the hospital, and explained the factors concerned in the production of the clinical syndrome manifesting itself as "Addison's disease" without adrenal pathology associated with the marked sodium ion loss present in the most productive external pancreatic fistula recorded. We have, in addition to this, outlined the factors involved in the alteration of the general electrolyte pattern and plasma protein values of this patient. Failure to correct these marked changes in fluid balance, electrolyte concentration and plasma protein values would have been lethal. Restitution of sodium ion associated with the administration of substances to maintain the ion in the circulating fluid volume, which must also be made adequate, will bring the individual to a metabolic normal. Physiologic saline, citrated whole blood and blood plasma, combined with a diet complete in various details will restore such an individual to a metabolic balance. Adequate amounts of the various vitamins, iron and calcium are indicated. The administration of a solution of sodium bicarbonate is unnecessary as bicarbonate ion is provided in satisfactory quantity as a by-product of the respiratory processes. As a matter of record, this unusually large fistula closed spontaneously upon restoration of the individual to a normal metabolic state, with particular reference to water balance, electrolyte pattern and plasma

protein concentration. Restoration of all three factors must be coordinated as it is impossible to individually correct one and achieve success.

OBSERVATIONS ON VOLUME FLOW ALTERATIONS INDUCED BY THE ADMINISTRATION OF VARIOUS SUBSTANCES INTO THE DUODENUM

During the period in which the patient was being restored to a normal metabolic state, a series of experimental studies were made. The first of these series of observations were conducted with a gastric and duodenal tube in place. Constant negative water suction was maintained on the gastric tube to prevent discharge of gastric contents into the duodenum.

TABLE VII

DETERMINATION ON PANCREATIC SECRETION*

	Carbon Dioxide Combining Power	Chloride
Control	60.76	66.2
225 cc. warm water	39.82	67.
225 cc. chicken broth	58.58	71.5
2 cc. 10 per cent HCL in 100 cc. water	73.33	60.5
50 cc. 10 per cent $NaHCO_3$	58.71	62.5
50 cc. olive oil	57.3	79.7
50 cc. 50 per cent glucose	30.33	57.

* All the above values are expressed in mEq./L. for pancreatic secretion showing alterations in crystalloid composition following administration of substances indicated through a duodenal tube.

Water

Two hundred twenty-five cubic centimeters of warm water was introduced into the duodenum through a duodenal tube. Regurgitation of water into the stomach did not occur, as fluid could not be aspirated through the gastric tube. A fall in the amount of pancreatic fluid from 12.4 cc. to 7.1 cc. and 7.4 cc. in successive 15-minute periods was observed. The acid gastric material was prevented from reaching the duodenum or was reaching it in extremely small quantity because of the constant suction supplied through the gastric tube. It is assumed that the duodenal contents were less acid due to dilution and that less stimulation to pancreatic secretion *via* the prosecretin mechanism resulted (Chart 3).

Hydrochloric Acid

It is well recognized that the introduction of acid gastric chyme into the duodenum will stimulate the flow of pancreatic juice through the pancreatic prosecretin-secretin mechanism. Therefore, we were not surprised that the deposition of hydrochloric acid directly into the duodenum produced an increase in the amount of pancreatic juice secreted. Thirty minims of 10 per cent hydrochloric acid in 100 cc. of warm water were introduced directly into the duodenum through a tube. The flow of pancreatic juice which had dropped to a low of 0.2 cc. in 15 minutes during the course of a series of experiments rose rapidly to 18.6 cc., and subsequently 16.4 cc. during the next 15-minute period. This series of events substantiated the fact that pancreatic flow is stimulated by the presence of acid in the duodenum in the human as it is in animals. These observations confirm those made by McCaughan,, Sinner and Sullivan,[20] in 1938 (Chart 3).

Sodium Bicarbonate

The counterpart of the administration of hydrochloric acid into the duodenum was undertaken by introducing 50 cc. of a 10 per cent solution of sodium bicarbonate through the duodenal tube. An immediate fall in secretion from 10.6 cc. to 6.1 cc. and 2.4 cc. was noted in successive 15-minute periods. The rise in p_H of the duodenal content reflected lessening of acid stimulus to secretion, caused drop in output (Chart 3).

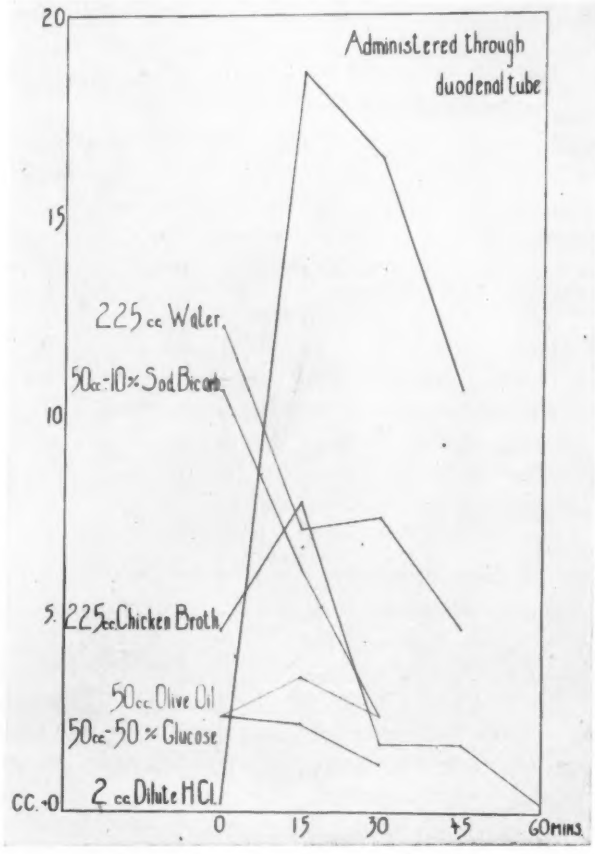


CHART 3.—Substances whose influence upon pancreatic secretion were to be observed were introduced into the duodenum *through the duodenal tube.*

Chicken Broth

Two hundred twenty-five cubic centimeters of chicken broth were introduced through the duodenal tube. The secretion rose from 4.6 cc to 7.8 cc., and then dropped, in successive 15-minute periods, to 1.7 cc., 1.7 cc. and 0.2 cc. A moderate increase in flow resulted initially. It is known that meat extracts and protein derivatives in chyme exert a secretagogue effect. The stimulus provided an increase in pancreatic flow which was short-lived (Chart 3).

Magnesium Sulphate
(Saturated Solution)

Fifty cubic centimeters of a saturated solution of magnesium sulphate was introduced into the duodenum through a duodenal tube. This was followed by a reduction of flow from 3.02 cc. in a 15-minute interval to 1.8 cc. of pancreatic secretion.

Olive Oil

Fifty cubic centimeters of olive oil was introduced into the duodenum through a duodenal tube. This was followed by a slight drop in external pancreatic secretion from 3.4 cc. in a 15-minute period to 2.4 cc. in a 15-minute period, without appreciable alteration in the determinations of chloride and bicarbonate contents in the secreted material.

These findings were contrary to those reported by McCaughan, Sinner and Sullivan,[20] in 1938; and by Comfort, Osterberg and Priestly,[6] in 1943.

Our conclusion from these results was that the introduction of olive oil into the duodenum produced no significant change either in the amount of pancreatic secretion or in the constituent electrolytes of the secretion (Chart 3).

Glucose

Fifty cubic centimeters of a 50 per cent solution of glucose was introduced into the duodenum through a duodenal tube. This was followed by a drop from 2.4 cc. in a 15-minute interval to 1.2 cc. of pancreatic secretion (Chart 3).

The second series of observations concerned themselves with the variations in flow through the fistula as a result of the *oral administration* of various substances (Chart 4).

Water

The result obtained with water administered by duodenal tube must be contrasted with that obtained when 225 cc. of warm water were given by mouth. Following this administration, we noted a slight rise from 23 cc. to 27 cc. and then a drop to 24 cc. in successive 15-minute periods. It is commonly recognized that water leaves the stomach almost immediately. In this instance, acid material was washed into the duodenum from the stomach with the water as a vehicle and consequently a rise in output resulted due to the lowered p_H of the duodenal contents (Chart 4).

Sodium Bicarbonate

Four grams of sodium bicarbonate given by mouth did not produce any appreciate effect upon volume flow of pancreatic secretion. The initial volume reading in a 15-minute interval was 24.2 cc. The subsequent readings at 15-minute intervals were 24.1 cc. and 22 cc. (Chart 4).

We concluded from this that sodium bicarbonate given in this quantity was insufficient to neutralize the stimulating effect of HCl upon the duodenal mucosa. The intubation experiment would indicate that repeated dosage with sodium bicarbonate would bring the p_H above the critical level of stimulation and would result in diminished secretion (See Chart 3). Prolonged administration of sodium bicarbonate was given in another of these

patients without appreciable change in carbon dioxide combining power. Control blood determinations were made for carbon dioxide and chloride in the blood on July 12, 1943. Subsequently, 16 Gm. of sodium bicarbonate

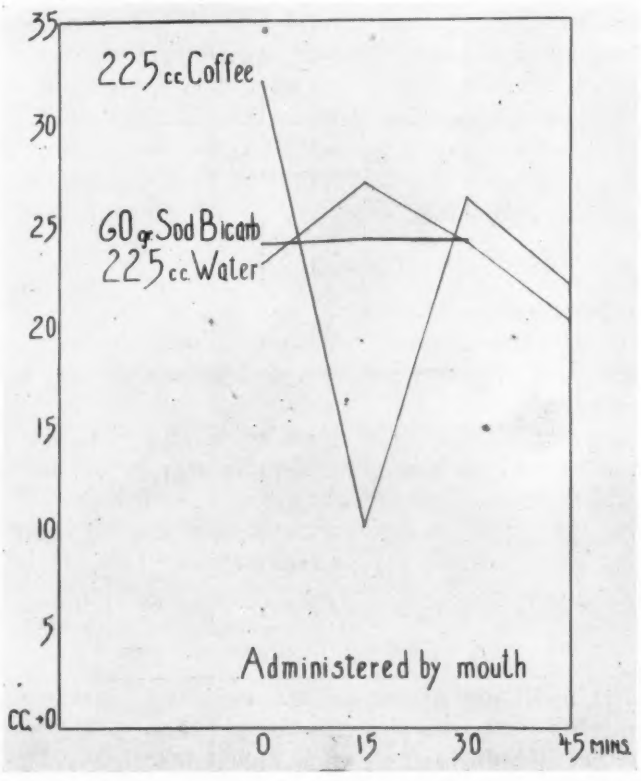


CHART 4.—Substances whose influence upon pancreatic secretion were to be observed which were given by mouth.

were given daily until a total dosage of 50 Gm. was obtained. Table VIII depicts the control and follow-up determinations:

TABLE VIII

Date	Carbon Dioxide Combining Power	Chloride
Control: (July 12, 1943)	30.5	98.0
(July 14, 1943)	32.6	91.2
(July 15, 1943)	34.1	99.6
(July 16, 1943)	35.0	101.2

Coffee

Two hundred twenty-five cubic centimeters of coffee given by mouth produced a drop in pancreatic secretion from a control standard of 32 cc. in a 15-minute interval to 10 cc., to 26.2 cc. and 21.8 cc. (Chart 4).

Sulfanilamide

The patient was given one gram of sulfanilamide by mouth, every 4 hours, for 12 doses. At the end of this time the concentration of the drug in the blood was 8.5 mg. per cent—in pancreatic secretion 7.0 mg. per cent. The first patient under similar therapy presented the following values: Blood—8.5 mg. per cent; pancreatic secretion—9.1 mg. per cent.

This afforded conclusive evidence that sulfanilamide was widely distributed throughout the pancreas, in concentration approximating that of its concentration in the blood, and that it is returned to the duodenum in pancreatic secretion in concentrations approximating that level obtained in the blood stream. This fact has been commented upon by other investigators.

Phenobarbital

Previous investigators (Coffey, Koppanyi and Linger)[4] found that barbiturates given in large, hypnotic and anesthetic doses produced a reduction in gastric and pancreatic secretion, and that barbiturate was excreted in the pancreatic juice.

Following the administration of phenobarbital 0.1 Gm., readings were observed in volume of pancreatic secretion from a control normal in 15 minutes of 11.6 cc., to subsequent readings of 14.2 cc., 16.0 cc., 19.6 cc. This slight rise was not considered significant. Barbital was not recovered from the secretion. These contradictory findings may have been due to the small dose of the drug employed.

Smoking (Cigarette)

The patient under observation did not use tobacco in any form. He, however, agreed to smoke two cigarettes for us.

The base line of pancreatic secretion was at this time 24 cc. in a 15-minute interval. Following smoking the volume of flow in the ensuing 15-minute interval was 20 cc. and in the next 15 minutes returned to 24 cc. (Chart 5).

Goodman and Gillman[11] state that the smoke of the average cigarette may yield 6–8 mg. of nicotine. This diminution of volume flow was considered to be a nicotine effect. The diminution of secretion was accompanied by some sweating.

THE EFFECT OF INTRAVENOUS FLUIDS UPON PANCREATIC SECRETION

The intravenous administration of 2,000 cc. of physiologic saline in two hours and 21 minutes resulted in a marked increase in the rate of pancreatic secretion. The base rate of secretion prior to the administration of the saline was 30 cc. in one hour. The average rate of secretion during the administration and for one hour subsequent to it was 60 cc. (Table IX).

In a similar manner, 5 per cent glucose in physiologic saline was administered. The base rate was 45.2 cc. per hour. The administration took 195

minutes and the patient was observed for 225 minutes, during which time he secreted 255 cc. of pancreatic juice. His hourly rate of secretion was 60 cc. (Table IX).

The secretory rate was increased markedly by augmented fluid intake. There was no essential difference between the administration of physiologic saline and 5 per cent glucose in physiologic saline (Table IX).

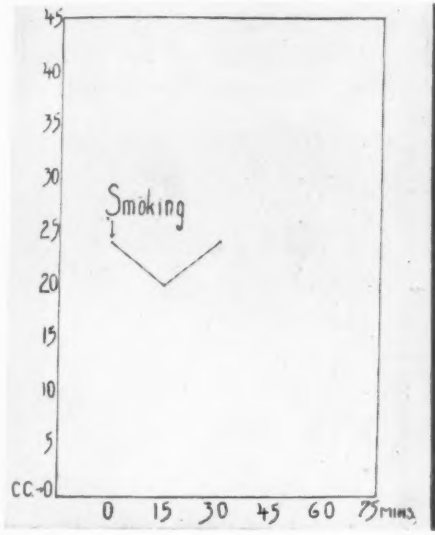


CHART 5.—The effect of smoking on pancreatic secretion.

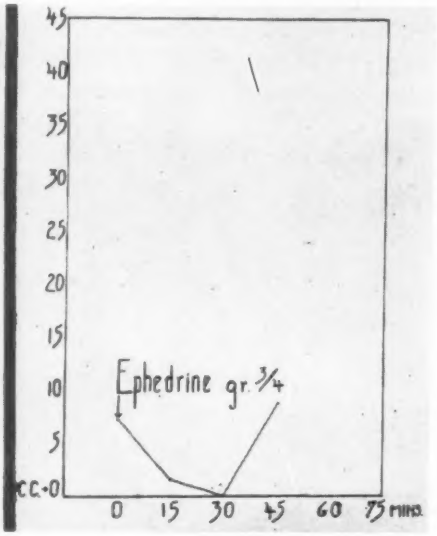


CHART 6.

TABLE IX

THE EFFECTS OF INTRAVENOUS ADMINISTRATION OF FLUID

Interval	Time	Saline I. V.	Pancreatic Inc. Vol.
60 mins.	12:00	.....	20.0 cc.
	1:00		
60 mins.	2:00	.....	24.0 cc.
25 mins.	2:25 started	.....	28.0 cc.
39 mins.	3:04	500 cc.	51.0 cc.
18 mins.	3:22	500 cc.	55.0 cc.
48 mins.	4:10	500 cc.	61.2 cc.
36 mins.	4:46	500 cc.	78.0 cc.
	5:46	.....	80.0 cc.
	6:43	.....	75.0 cc.
	5 PER CENT — GLUCOSE IN SALINE		
60 mins.	12:00	.....	43.2 cc.
	1:00		
60 mins.	2:00	.....	47.2 cc.
	2:25		
71 mins.	3:36	500 cc.	60.0 cc.
28 mins.	4:04	500 cc.	62.0 cc.
43 mins.	4:47	500 cc.	48.8 cc.
53 mins.	5:40	500 cc.	52.0 cc.
	6:10	.....	32.0 cc.

OBSERVATIONS ON VOLUME FLOW ALTERATIONS INDUCED BY THE ADMINISTRATION OF DRUGS SUBCUTANEOUSLY

Ephedrine

The intramuscular administration of 0.75 grain of ephedrine resulted in a marked inhibition of pancreatic secretion over a period of approximately 30 minutes, with a gradual return to normal at the end of 45 minutes. The diminution in flow was the result of a decrease in minute volume flow of blood through the pancreas, and this was due to the vasoconstrictor action of the drug. The concentration of chloride and bicarbonate in the pancreatic secretion showed a slight decrease from the preliminary control value.

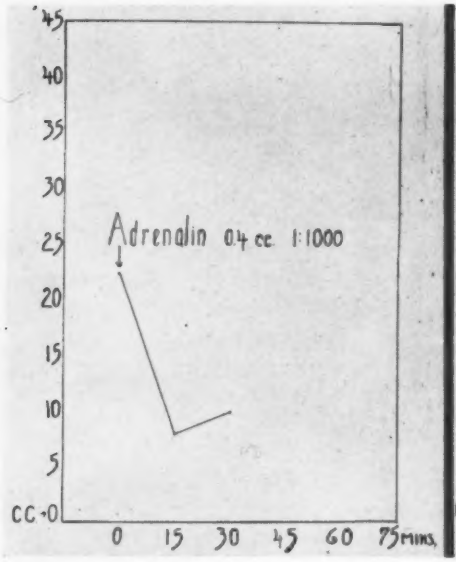


CHART 7.

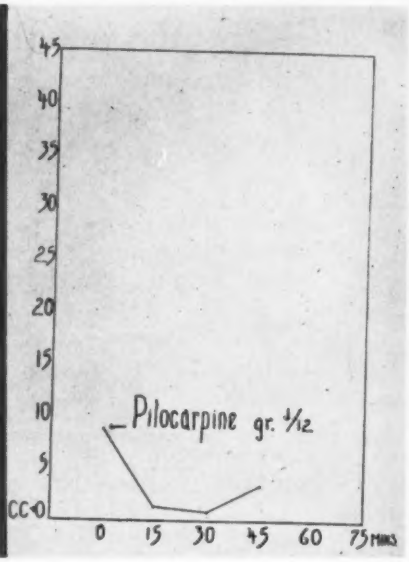


CHART 8.

Adrenalin

The intramuscular injection of 0.4 cc. of 1:1000 solution of adrenalin resulted in an abrupt diminution of pancreatic secretion, reaching its maximum effect in 15 minutes, after which a gradual increase in flow was noted. This diminution in flow was the result of the vasoconstrictor action of the drug, which produced a decrease in minute volume flow of blood through the pancreas.

Pilocarpine

The patient under study was given 1/12 gr. of pilocarpine intramuscularly. This administration was made after a base-line of pancreatic flow had been established. The usual peripheral effects of the drug were soon observed. The result was dramatic. He had copious perspiration, marked salivation, the urge to defecate and urinate; his pupils were dilated; he was shaky and apprehensive. Pancreatic secretion dropped from 9 cc. to 1 cc.; to 1 cc.;

to 3.5 cc.; in successive 15-minute periods. (This experiment was done three times with identical results.) There was a consistent drop of total bicarbonate concentration in the pancreatic juice, following the administration of pilocarpine.

Pilocarpine produces its effect by a highly specific action on cells innervated by postganglionic cholinergic fibers. This action is directly on the cholinergic substance (Goodman and Gillman[11]). The action should be the same as obtained on electrical stimulation of the vagus in the laboratory animal; yet, a different result is obtained.

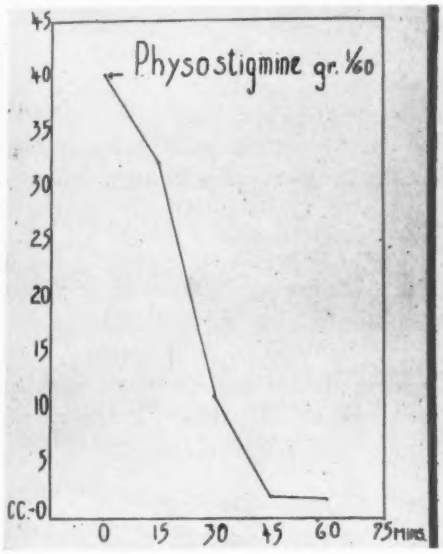


CHART 9.

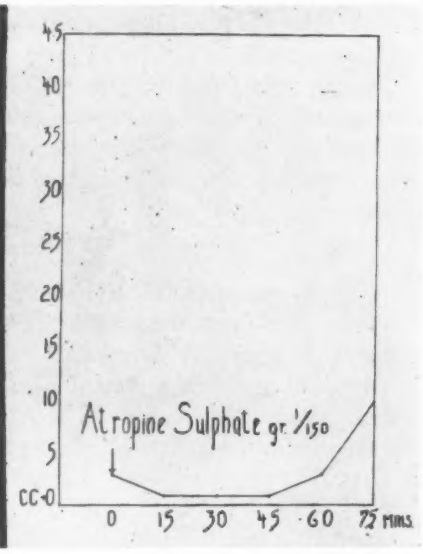


CHART 10.

It would seem that where we had muscarinic stimulation on the pancreas plus increased flow of acid gastric juice providing an indirect stimulation (secretin mechanism), a combination of the two mechanisms would cause an increase in the production of pancreatic juice. This did not occur, and, therefore, did not fulfill our expectations based upon the previously described action of pilocarpine.

Physostigmine

Some help in analyzing the deviation from the expected result after the administration of pilocarpine may be obtained from the following: Physostigmine, grain 1/60, was injected intramuscularly, and the flow in 15-minute periods was, successively, 40.0 cc.; 32 cc.; 11.2 cc.; and 1.6 cc.

It is known that physostigmine exerts its pharmacologic activity in the body by inhibiting cholinesterase in body fluids and tissues (Goodman and Gillman[11]). This esterase is responsible for the rapid and continuous destruction of acetylcholine. Thus, physostigmine protects acetylcholine from enzymatic hydrolysis. The responses obtained by the injection of physostigmine should

be the same as those from acetylcholine. It should be recalled that the presence of acetylcholine is necessary for the action of physostigmine.

It is also necessary to recall that acetylcholine produces both muscarinic and nicotinic effects. Acetylcholine is a mediator of nerve impulses, causing the secretion of epinephrine. Stewart and Rogoff[24] demonstrated this when they found that the epinephrine content of the blood increased to as much as fifteen times the normal after the administration of physostigmine. Thus, the reduction of flow from the administration of physostigmine is understandable. Epinephrine is released and by vasoconstriction diminishes the flow of blood through the substance of the pancreas, thereby reducing the flow of pancreatic juice. This occurs notwithstanding the fact that physostigmine by its muscarinic action should produce some increase in pancreatic flow.

Having considered the effect of physostigmine, it may be that pilocarpine has a mixed effect and produces both the muscarinic and some of the nicotinic effects of acetylcholine. Accordingly, it is suggested that epinephrine may be released when pilocarpine is injected and that the former causes the diminution in pancreatic output.

Atropine

Atropine caused a definite decrease in the amount of pancreatic secretion in a very short time. Pancreatic secretion decreased from 18.4 cc. to 1.8 cc.; to 0.0 cc. in 15-minute intervals.

Atropine produces a reduction of gastric motility and secretion, with an ensuing diminution in activation of prosecretin. Therefore, the principal effect is through an indirect mechanism (Farrell and Ivy[9]).

Morphine

Morphine is a definite depressant upon pancreatic secretion. The effect is produced indirectly. The gastric secretion of hydrochloric acid is retarded. Gastric motility is lessened and the tone of the antral portion of the stomach is increased. The pyloric sphincter is contracted. The total effect causes a slowing in the passage of gastric content into the duodenum. The reduction in amount and the delay in passage of acid-gastric chyme into the duodenum results in the formation of a smaller amount of secretin, and, thus, the production of less pancreatic juice.

The patient was given 0.25 gr. of morphine sulfate intramuscularly after a base line for secretion had been established. Flow dropped from 14 to 3 cc. in a period of 15 minutes, with a gradual rise in the quantity of pancreatic juice secreted during the ensuing period.

Histamine

The patient was given 1 cc. of 1:1000 histamine phosphate subcutaneously after a base level of pancreatic secretion of 22.0 cc. in 15 minutes had been established. Following this there was a fall to 12.5 cc. in 15 minutes, after which the secretion rapidly increased to 28.0 cc., and subsequently to 40.0 cc. in ensuing 15-minute intervals.

We have no explanation for the initial diminution of secretion. The

subsequent rise is due to the established action of histamine in increasing gastric acid secretion and increased gastric motility, with consequent stimulation to the secretin mechanism.

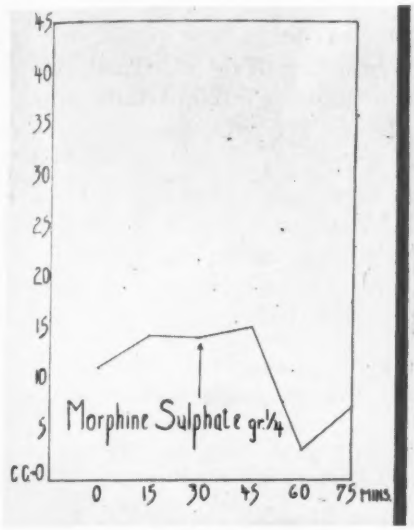


CHART 11.

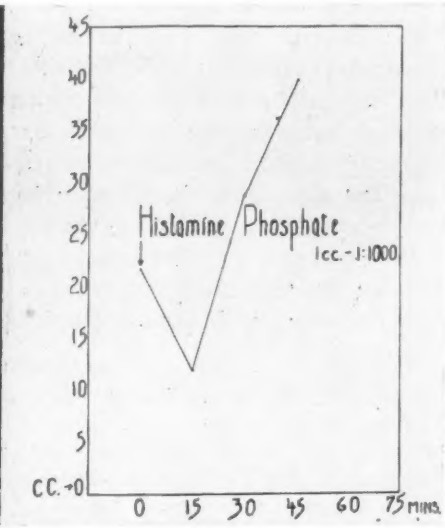


CHART 12.

SUMMARY

1. Detailed observations upon three patients with external pancreatic fistulae have been presented. One of them produced 1770 cc. in a 24-hour period.

2. Attention has been drawn to the marked alteration in water balance, plasma protein level and plasma electrolytes, with special emphasis upon plasma sodium in patients with severe external pancreatic fistula.

3. It has been emphasized in this presentation that the sodium loss in severe pancreatic fistulae produces a clinical syndrome similar to that described by Addison, with the exception that in these individuals adrenal disease is not present. This analogy has not been previously stressed.

4. The administration of adequate amounts of sodium and water in the presence of sufficient plasma protein to hold them in the circulation alleviates the symptoms peculiar to this syndrome.

5. Diminution in pancreatic secretion through the fistula may be obtained by the administration of a number of drugs. However, ephedrine and sodium bicarbonate are the most practical of these because of the unpleasant or deleterious side-effects of the others.

6. Detailed physiologic observations upon pancreatic function have been recorded. Certain of these observations contribute definite support to the theory that secretin secretion is a filtration process. These are:

a. Sodium ion is present in equal amounts in both blood plasma and pancreatic secretion.

b. The total of the concentrations of chloride and bicarbonate ions are the same in blood plasma and pancreatic secretion.

c. The same amount of ionizable calcium is present in blood plasma and pancreatic secretion.

d. Sulfanilamide is found in the same amount in blood plasma and pancreatic secretion.

7. Pancreatic flow is continuous throughout the 24-hour period, and is influenced, to great degree, by the state of hydration of the individual.

8. Large amounts of ionizable calcium are normally returned to the gastrointestinal tract through pancreatic secretion. This phenomenon has not previously received the recognition it warrants.

9. The appearance of sulfanilamide in therapeutic concentration in pancreatic secretion suggests its use in acute inflammatory disease of the pancreas.

10. Pancreatic secretion is markedly stimulated by the administration of histamine intramuscularly, and by the intravenous administration of physiologic saline or 5 per cent glucose in physiologic saline, intravenously.

BIBLIOGRAPHY

1 Bayliss, W. M., and Starling, E. H.: Quoted by McCaughan and Purcell.[18] Arch. Surg., **43**, 269, 1941.

2 Bernard, C.: Quoted by McCaughan and Purcell.[18] Arch. Surg., **43**, 269, 1941.

3 Best, C. H., and Taylor, N. B.: Physiological Basis of Medical Practice. Williams and Wilkins Co., Baltimore, 1943.

4 Coffey, R. S., Köppanyi, T., and Linger, C. R.: Amer. Jour. of Digest. Dis., **7**, 21–23, January, 1940.

5 Comfort, M. W., and Osterberg, A. E.: Amer. Jour. of Digest. Dis., **8**, 337–40, 1941.

6 Comfort, M. W., Osterberg, A. E., and Priestly, J. T.: Amer. Jour. of Digest. Dis., **10**, 7–20, January, 1943.

7 Comfort, M. W., and Priestly, J. T.: Proc. Staff Meetings Mayo Clinic, **18**, 409–416, November 3, 1943.

8 Craft, C. B.: Surgery, **4**, 64–73, July, 1938.

9 Farrell, J. I., and Ivy, A. C.: Amer. Jour. Physiol., **78**, 325–38, October, 1926.

10 Gamble, J. L.: Chemical Anatomy, Physiology and Pathology of Extracellular Fluid. Harvard Med. School, 1942.

11 Goodman, L., and Gillman, A.: The Pharmacological Basis of Therapeutics. The Macmillan Co., N. Y., 1941.

12 Ivy, A. C.: Amer. Jour. Physiol., **46**, 420–42, 1918.

13 Komarov, S. A., Langstroth, G. O., and McRae, D. R.: Canad. Jour. Research, **17**, 113–23, May, 1939.

14 Krogut, B., Matzner, M. J., and Sobel, A. E.: Jour. Clin. Inves., **15**, 393–96, July, 1936.

15 Loeb, R. F., *et al.*: Jour. Exper. Med., **57**, 775, 1933; *idem*, *ibid.*: **90**, 496, 1939.

16 McCance, R. A.: Experimental Sodium Chloride Deficiency in Man. Proc. Royal Society, **119**, 245–68, 1936.

17 McCance, R. A., and Widdowson, E. M.: Bio. Chem. Jour., **33**, 523–29, 1939.

18 McCaughan, J. M., and Purcell, H. K.: Arch. Surg., **43**, 269–83, August, 1941.

19 McCaughan, J. M., and Sinner, B. L.: Arch. of Surg., **35**, 449–60, September, 1937.

20 McCaughan, J. M., Sinner, B. L., and Sullivan, S. C.: Arch. of Int. Med., **61**, 739–54, May, 1938.

21 McClure, C. W.: Rev. Gastro-enterol., **3**, 1–26, 1936.

22 Pavlov, I. P.: Quoted by McCaughan and Purcell.[18] Arch. Surg., **43**, 269, 1941.

23 Snyder, W. H., and Lium, R.: Surg., Gynec. & Obst., **62**, 57–64, 1936.

24 Stewart, G. N., and Rogoff, J. M.: Jour. Pharmacol. & Exper. Therapy, **17**, 227–248, 1921.

THE HEALING OF SURFACE CUTANEOUS WOUNDS: ITS ANALOGY WITH THE HEALING OF SUPERFICIAL BURNS*

JOHN MARQUIS CONVERSE, M.D.†
NEW YORK, N. Y.

AND

A. H. T. ROBB-SMITH, M.D.‡
OXFORD, ENGLAND

INTEREST in the healing of cutaneous wounds produced by the removal of skin grafts was aroused by the fact that the wounds of superficial burns appeared to present a similar process of healing. Brown and McDowell[1] made the same observation, and later Cannon and Cope[2] used skin graft donor areas to test the effect of coagulants on epithelial growth.

Four hundred and sixty-nine skin graft donor areas were studied. These skin grafts were removed for use in plastic operations and for the covering of raw areas created by burns or trauma. Three types of skin grafts were employed: Thin Thiersch grafts and thicker split (intermediate) grafts which were removed with the Blair skin graft knife. Skin grafts of varying thickness (0.010–0.042 inches) were cut with Padgett's dermatome. The donor sites used were the medial aspect of the arm, the abdomen, the back and the thigh. A few grafts were removed from other regions of the body. The routine post-operative treatment of the donor areas was as follows: Gauze soaked in $\frac{1}{1000}$ adrenaline solution and large saline packs were held with pressure against the bleeding donor area. Then strips of fine-meshed vaselined gauze, impregnated with sulfanilamide powder, were applied to the wound and covered by gauze, cotton and a pressure bandage firmly anchored by adhesive. The dressings over the skin graft donor areas were removed when the latter were healed. The approximate healing time of these donor areas was observed, the dressing being removed when the vaselined gauze could be easily detached from the new epithelial surface of the area. It is obvious that accurate comparative data are difficult to obtain because the thickness of the graft, which is cut with the dermatome, varies greatly with the thickness of the cement which is employed to produce adherence of the skin to the dermatome drum, because of individual variations in the characteristics of the skin of the different patients, and because of variations of the age and general condition of the patients. It is felt, however, that observations in a sufficient number of cases (469) have permitted us to formulate the following conclusions:

1. *The quality of the repair was roughly proportional to the rapidity of healing:*

Donor areas, healing in six to ten days, failed to leave more than a pink area, which rapidly became pale, leaving a faintly visible scar with a soft

* Sections of this paper were read by Dr. Converse before the Moynihan Surgical Club, July 26, 1942, Oxford, England.

† From the American Hospital in Britain (Churchill Hospital), Oxford. At present Capt. M.C., U.S.A.

‡ From the Radcliffe Infirmary, Oxford. Reader in Pathology, University of Oxford.

pliable base. Donor areas, healing in 14 to 21 days, left a more visible, uneven scar with a harder base. Some donor areas remained unhealed for a longer period, and often left retracted, hypertrophic scars.

2. *The rapidity of healing appeared to be dependent upon a number of factors:*

A. *The Thickness of the Graft:*

(1) After removal of thin Thiersch grafts at about the level AB in Fig. 1, healing was achieved in six to ten days.

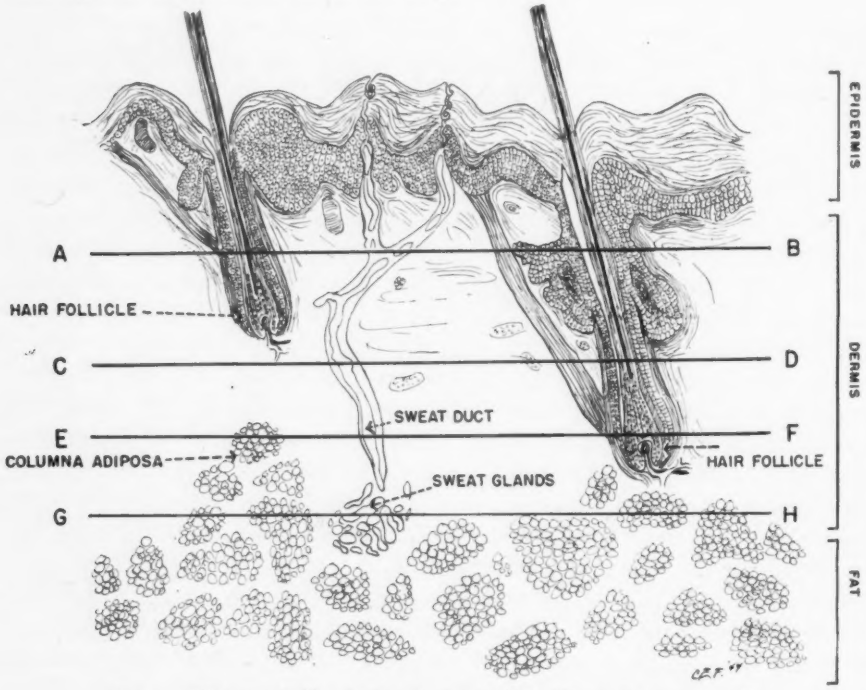


FIG. 1.—Diagram of skin showing levels at which skin grafts are removed. AB, level of a Thiersch graft; CD, level of an intermediate split-graft. EF, level of a thick graft; GH, level of a full-thickness skin graft.

(2) After removal of split (intermediate) grafts at about the level CD (Fig. 1), healing occurred generally within 14 days.

(3) When grafts were cut along the level EF, towards the base of the dermis, or along the level GH (Fig. 1), at which lobes of fat began to appear, healing was much slower, taking from 21 to 58 days.

B. *The Thickness of the Skin of the Donor Site:*

In four patients, 0.016-inch dermatome grafts were removed simultaneously from the abdomen and from the inner aspect of the thigh. The abdominal areas, in which the dermis is thicker, healed more quickly (average 12 days) than the thigh areas (average 16 days).

C. *The Degree of Looseness of the Skin of the Donor Area:*

In donor areas in which the skin is loosely bound-down to the underlying structures, healing occurred more rapidly by contraction.

D. *Infection:*

In seven cases gross infection with suppuration were noted in the donor area. Cultures were not made. In each case, the dressing, maintained by a bandage, had slipped, failing to protect and immobilize the wound.

In six donor areas from which very thick grafts had been removed, infection was observed after the 23rd day. As a result of the infection,

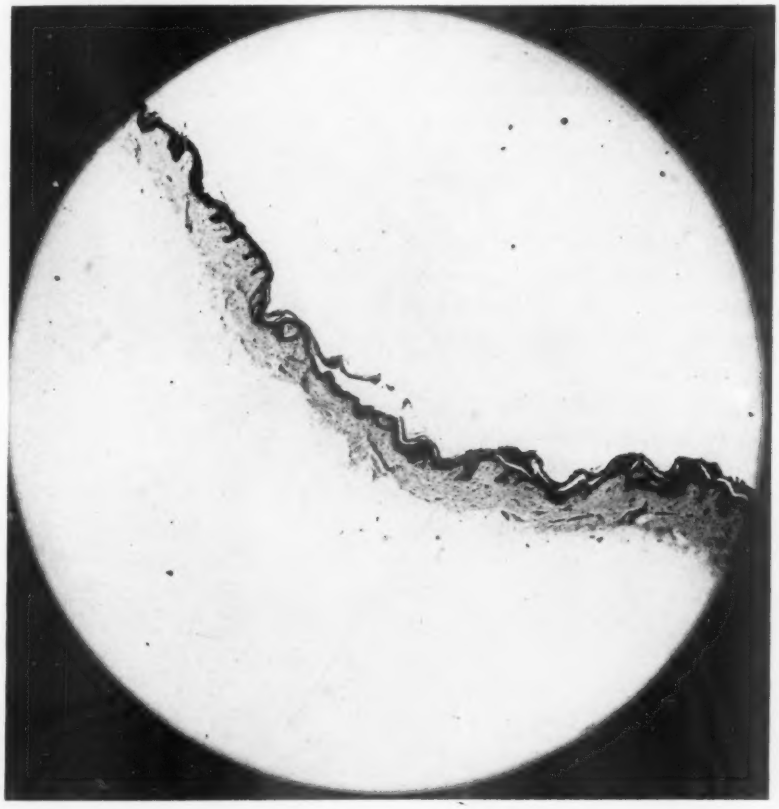


FIG. 2.—Thin graft (0.25 mm.—0.01-in.) removed from the abdomen (about 0.008 on the dermatome calibration) when fixed and embedded showing a portion of the dermis removed. HE × 20 (R.I.S.H. 1585 (6) (42)

necrosis of the remaining dermis was observed which resulted in sloughing followed by granulation of these areas. Healing occurred slowly (average healing time 52 days) leaving an hypertrophic, rough and contracted scar.

PROCESS OF HEALING OF SKIN GRAFT DONOR AREAS

The process of healing of such areas was studied in four patients, who were undergoing a series of plastic operations, and who consented to the removal of biopsies from healing donor areas at various time intervals.

The healing of cutaneous wounds is a dual process, a combination of repair with contraction.

1. *Process of Repair:*

A. *Source of Epithelium* (Figs. 2–10):

The epidermis is removed with the skin graft so that the new epithelial surface must originate from the epithelial elements in the dermis (Figs. 2–8), except from the edges of the defect where there will be regeneration from the surrounding normal epidermis attempting to cover the bare area.

In the study of epithelial repair, histologic sections have revealed the following facts:

1. In the healing of donor areas, the sebaceous glands participate, together with the hair follicles, in the reepithelization (Figs. 3–7).

2. The hair follicles are the main source of epithelium (Figs. 3–8).

3. The sweat ducts, running up from the sweat glands (which are situated in clusters at the base of the dermis between the lobes of fat), help to furnish epithelium when grafts are cut in the depth of the dermis. The sweat duct epithelium does not furnish as much epithelium as an occasional remaining hair follicle, and regeneration is much slower (Figs. 9 and 10). It is to be noted that the hair follicles diminish in number as the deeper layers of the dermis are reached, as many hair follicles are implanted superficially. Horizontal sections through the dermis at different levels demonstrate this fact (Figs. 11, 12 and 13).

This decrease in available epithelium can be demonstrated when cutting skin grafts with the dermatome at different levels. When a thin graft is cut, innumerable small bleeding points are seen. They are the transversely sectioned anastomotic vessels of the skin and are separated by areas of connective tissue containing a hair follicle (Fig. 11). As thicker grafts are cut, the bleeding points become coarser and more widely spaced, and the hair follicles are also more widely separated. Near the base of the dermis, protrusions of fat appear, due to the irregular junction of the fat with the dermis (Fig. 13). The junction between the dermis and the subcutaneous fat is not an even one. Numerous projections of fat, the "columnae adiposae" are seen; they join the base of the hair follicles, implanted at various levels in the dermis (Fig. 1). The numerous islands of fat thus formed in the dermis facilitate contraction during the healing of dermal wounds.

It, thus, results that epithelization takes place from numerous islands of epithelium, which tend to join each other by cellular multiplication and migration. The more numerous these islands are, the more rapid the healing will be.

B. *The formation of fibrous tissue and its influence on the quality of the epithelium:*

Sections removed from donor areas which have healed rapidly (Fig. 14), show a good quality epithelium over a thin layer of loose connective tissue. This layer is relatively avascular and elastic fibers do not develop until epithelial healing has been complete for some time. Even after five weeks, only very fine fibers are present (Figs. 15, 16 and 17).

When healing has been slow, the appearance is quite different (Fig. 18). Under a thin flat atrophic epithelium, under which there is little rete peg formation and presenting few or no hair follicles, is a thick layer of hori-

FIG. 3

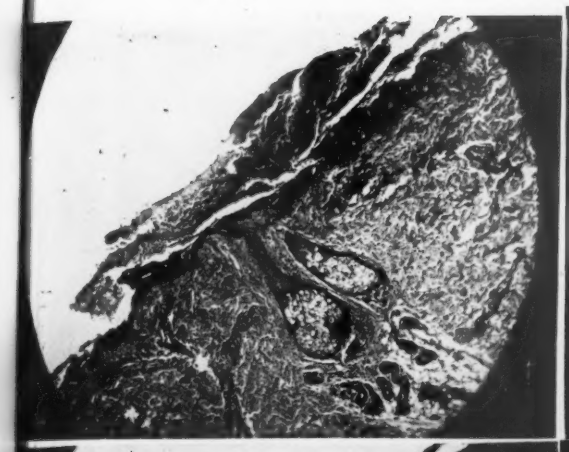
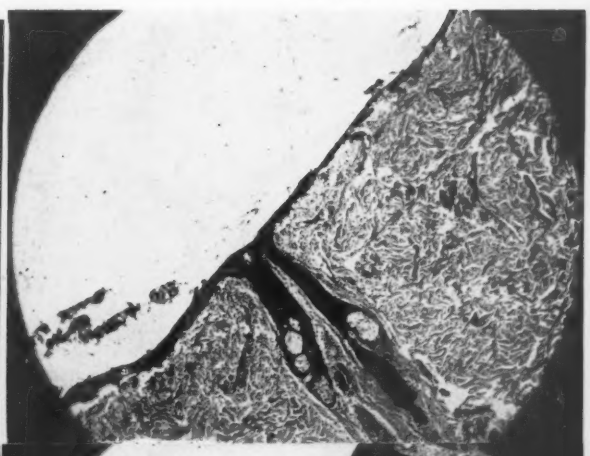
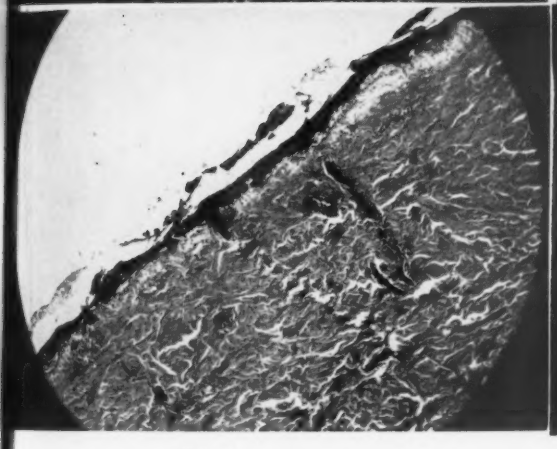


FIG. 4





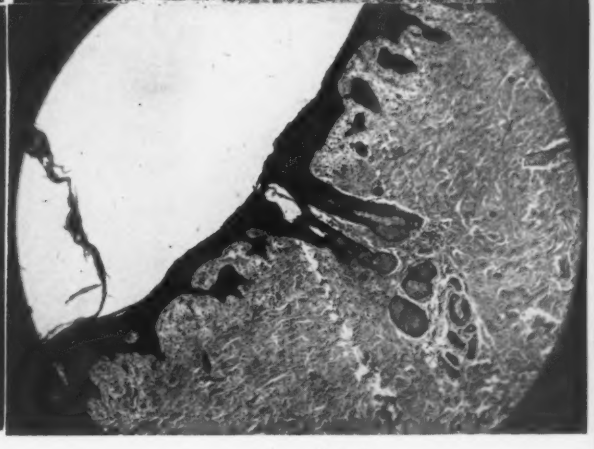


FIG. 5

FIG. 6

FIG. 3.—Donor area two days after removal of a thin graft showing commencing epithelial regeneration from the mouth of a hair follicle and from the sebaceous glands. HE × 40 (R.I.S.H. 1476 (4) (42)

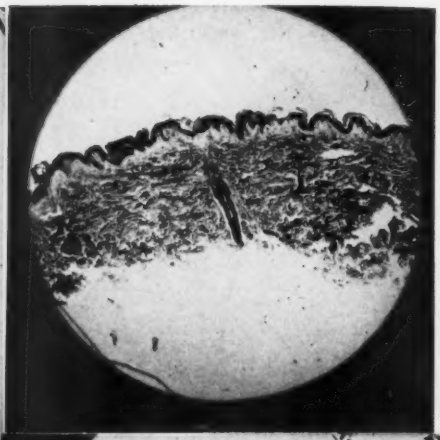
FIG. 4.—Donor area three days after removal of a thin graft showing the epithelial sheet spreading out from a hair follicle. HE × 40 (R.I.S.H. 1606 (1) (42)

FIG. 5.—Donor area five days after removal of a thin graft. Epithelial regeneration is complete, the epithelium is thicker than in Figure 4. There is a suggestion of rete peg formation and loose subepidermic connective tissue can be seen, particularly at the right hand end of the section. HE × 40 (R.I.S.H. 1606 (3) (42)

FIG. 6.—Donor area nine days after removal of a thin graft. Epithelial regeneration is complete, the epithelium is much thicker than in Figures 4 and 5. There is keratinization and well-marked, though irregular rete pegs. The newly formed loose subepidermic connective tissue is well shown. HE × 40 (R.I.S.H. 1476 (6) (42)

FIG. 7

FIG. 8



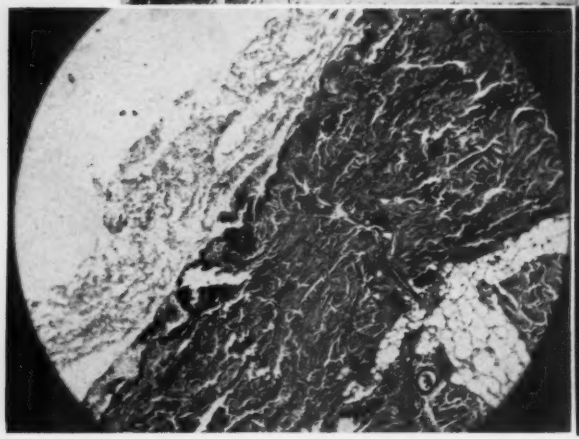


FIG. 9

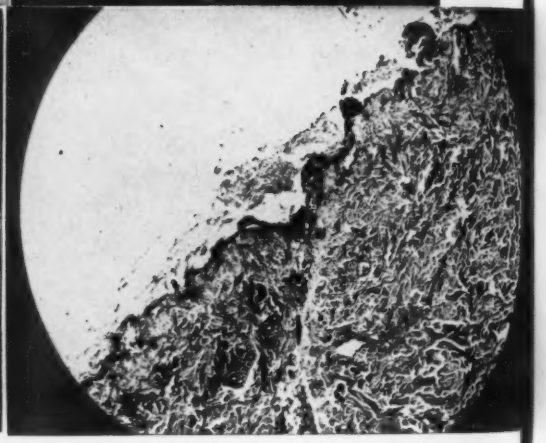


FIG. 10

FIG. 7.—Comparison of healed donor area with an autograft after 12 days. Immediately after the thin graft had been removed a portion of it was reapplied and the rest of the donor area was allowed to heal. At the extreme right hand, a portion of the normal skin can be seen, then there is the area of regenerated epidermis with irregular rete pegs and loose subepidermic connective tissue, then a nodule where the regenerating epithelium has grown under the graft, then the autograft itself; and the granulating zone can just be made out. HE × 7.5. (R.I.S.H. 1585 (1) (42)

FIG. 8.—Thick graft (1.36 mm., 0.05-in.) removed from abdomen (about 0.032 on dermatome calibration) when fixed and embedded showing the removal of the dermis and of the hair follicles. HE × 20 (R.I.S.H. 1585 (5) (42)

FIG. 9.—Donor area three days after removal of a thick graft, only occasional minute islands of epithelium can be seen around the sweat ducts. (Compare with Figure 4). HE × 40 (R.I.S.H. 1606 (2) (42)

FIG. 10.—Donor area five days after removal of a thick graft; most of the donor area is bare and there is only a small island of epithelium arising in relation to a sweat duct. (Compare with Figure 5). HE × 40 (R.I.S.H. 1606 (4) (42)

zontally arranged collagen fibrils, completely deficient in elastica (Fig. 19) and the whole dermis is poorly vascularized. These facts explain why these scarred areas present a hard base, why the epithelium is prone to fissure and ulcerate after trauma, and Brown[3] has also suggested that a factor in the liability to trauma is the lack of tethering of the epithelium due to the deficiency in rete pegs.

2. Process of Contraction:

All healing wounds contract. Cutaneous wounds, such as donor areas, heal mostly by epithelization and little by contraction. Measurements of the degree of contraction of the wound after the removal of skin grafts were made by comparing (in 62 patients) the size of the piece of skin on the dermatome drum with the size of the healed donor area.

Very little contraction occurs (2–5 per cent) in the donor areas until very thick grafts are removed. Contraction increases to (5–10 per cent) and may reach as high as 20 per cent when the grafts are cut in the base of the dermis where fat begins to appear.

Infection and mechanical and chemical irritation delay epithelial healing, and contraction is increased. We have already noted that contraction occurs more readily when the skin of the donor area is loosely bound down to the underlying tissues. This contraction of the wound is most marked along the direction of the lines of the skin (Langer's lines).

CONCLUSIONS

THE "INTER-ISLAND CONTRACTION"

It would appear that epithelial resurfacing originates from the individual epithelial islands formed from each hair follicle, sweat duct or cluster of sweat glands. Each epithelial island endeavors to join its neighbors not only by cellular division and migration but also by contraction (inter-island contraction). The longer epithelial healing takes to resurface the wound, the more marked this inter-island contraction will be. Such a delay in healing was observed in donor areas, in which the dermis was transected near its base; this was apparently due to the diminution in the number of elements of available epithelium, but infection, and mechanical and chemical irritation produce the same retarding effect. In such cases, a thick layer of relatively avascular inelastic fibrous tissue is laid down which is covered by an atrophic epithelium of poor quality (Figs. 18 and 19).

HEALING OF SUPERFICIAL BURNS

In the past there has been a tendency to attribute success or failure of local burn treatment to the type of treatment used. According to some, the use of certain chemicals over the burn wound has resulted in "healing without scars" of burns. It is true that the necessity of treating the burn with full-thickness skin loss, by early skin grafting is now generally recognized. However, it would appear that within the group of burns generally classified as second degree burns, variations in the quality of the healing of these areas depend upon the extent of the tissue destruction.

FIG. 11

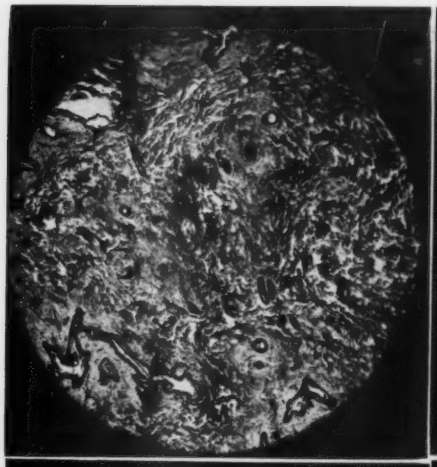
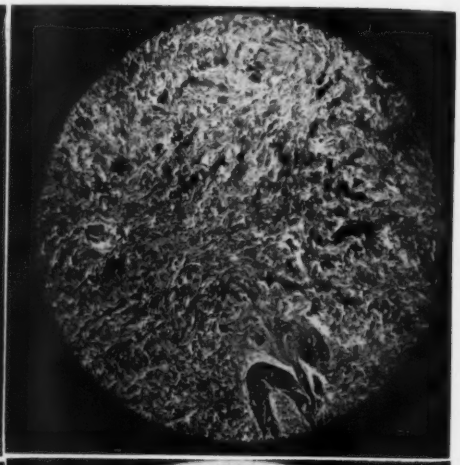
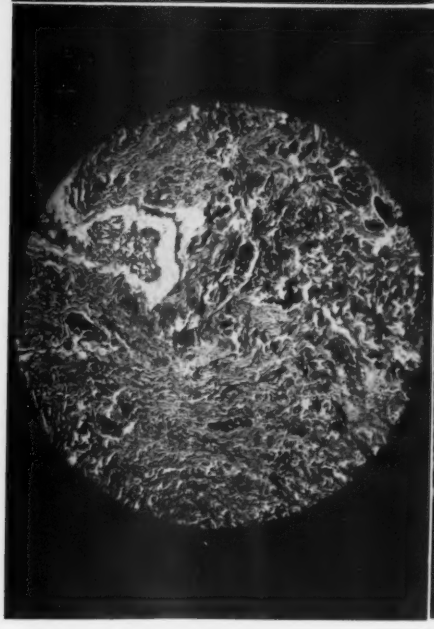


FIG. 12





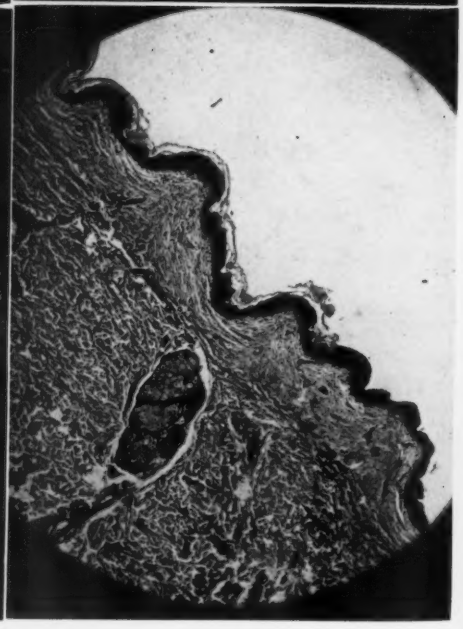


FIG. 13

FIG. 14

FIG. 11.—Horizontal section of skin of thigh below the epidermic surface, cut 0.18 mm. (about 0.007-in. on the dermatome calibration) when fixed and embedded. The openings of the hair and sweat glands can be seen, also a portion of the epithelium where the deeper epithelial folds occur. HE × 20 (R.I.P.M. (345/43)

FIG. 12.—Horizontal section of skin of thigh, below the epidermic surface, cut 0.36 mm. (about 0.028-in. by the dermatome calibration) when fixed and embedded. There are no hair follicles and the sweat ducts can only be made out with difficulty and are scanty. HE × 20 (R.I.P.M. 345/43)

FIG. 13.—Horizontal section of skin of thigh, below the epidermic surface, (about 0.034-in. by the dermatome calibration) when fixed and embedded. The coiled sweat glands are seen as well as intradermic protrusions of fat. HE × 20 (R.I.P.M. 345/43)

FIG. 14.—Healed donor area 32 days after the removal of à thin graft. The epidermis is keratinized and of moderate thickness. Rete pegs are not marked but there is the normal undulation of the skin, and hair follicles. The contrast between the new-formed subepidermic connective tissue which is becoming collagenized and the coarse collagen fibers of the original dermis can be clearly seen. (Compare Figures 6 and 18). HE × 40 (R.I.S.H. 1476 (3) (42)

During two years' service at the American Hospital in Britain (1940–1942) 191 burns were observed. These burns were seen at all stages, some as early as two hours after injury, others after complete healing, often because of the need for secondary plastic operations. The youngest patient was age 5 the oldest, 64. The patients were civilians as well as belonging to the Armed Services. The causes of the burns were variable; 143 were related to the War (gasoline explosions, plane crashes, incendiary bombs, flash burns of high explosives, accidents in war industries); 48 were of the usual civilian type. Early treatment had often been carried out in other hospitals, and the methods of local treatment employed were very variable: irrigation methods (saline baths, irrigation envelopes); coagulation methods (tannic acid and silver nitrate, gentian violet, triple dye, sulfadiazine in triethylanolamine); lightly applied dressings of wide-mesh vaselined gauze (*tulle gras*) and moist saline dressings; pressure dressings with fine-mesh vaselined gauze; plaster encasements and splints. The healing of these burn wounds was observed, and 63 biopsy specimens were removed for histologic examination.

In defining the depth of the burn, it would seem more logical to use anatomic terms. Table I shows the terminology used in this paper.

TABLE I

CLASSIFICATON OF BURNS

Superficial Burns (partial skin loss)	*Epidermal burns:* Erythema. Epithelial desquamation.	Heal well.
	Dermal burns: Blistering. Destruction of superficial layers of the dermis.	
	Deep dermal burns: Destruction of the dermis down to the deep layers.	Heal slowly, with contraction; may require skin grafting.
	Mixed burns: Small areas of total skin loss alternate with areas of deep dermal burns.	
Deep Burns (total skin loss)	Destruction of the whole-thickness of the skin into, or beyond, the fat.	Heal with difficulty, producing contractions and deformities. Skin-grafting the rule.

1. *Epidermal Burns.*—These burns are characterized by erythema, often followed by an epithelial desquamation. A detailed study of the early histologic changes in experimental burns has been made by Leach[4] and exactly comparable changes have been observed in man.

2. *Dermal Burns.*—Blistering is the rule. In the histologic sections studied, blisters were due to an epidermo-dermal separation produced by the exudation of fluid. In one section, the layer of separation was deeper than the junction of epidermis and dermis, in the dermis itself.

When the base of the blister is red, smooth and moist, healing may be expected in the absence of infection in 7–10 days. Epithelization in such superficial burns originates, possibly from a few remaining islands of basal epithelium, and from the hair follicles and the sweat ducts. The histologic picture is the same as that observed in the healing of a donor area after the removal of a thin skin graft (Figs. 3–6 and 14–17).

When the base of the blister is grey and dry, the dermis is more deeply involved, and healing will be slower because a layer of burned dermis must first be eliminated as a slough. Histologic examination has shown that

FIG. 15

FIG. 16

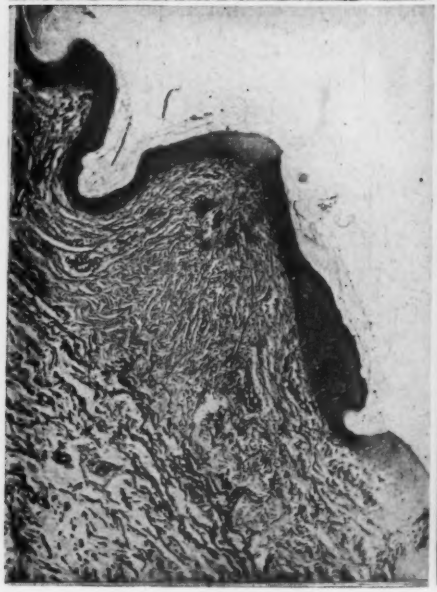


FIG. 17

FIG. 18

FIG. 15.—Normal skin to show elastic fibers. There is an imperceptible transition from the coarse fibers of the dermis to the fine fibers of the subepidermic region. Orcein × 120 (R.I.S.H. 1585 (1) (42)

FIG. 16.—Healed donor area 12 days after removal of a thin graft from the abdomen (0.008-in. by the dermatome calibration). The elastic fibers of the original dermis can be clearly seen, but no elastic fibers have developed in the newly-formed, subepidermic loose connective tissue. Orcein × 120 (R.I.S.H. 1585 (1) (42)

FIG. 17.—Healed donor 32 days after removal of a thin graft from the abdomen (0.008-in. by the dermatome calibration). The elastic fibers of the original dermis can be clearly seen and very fine elastic fibers have developed in the new-formed subepidermic connective tissue. (Compare with Figures 14-16). Orcein × 120 (R.I.S.H. 1476 (3) (42)

FIG. 18.—Healed hypertrophic-scarred donor area 65 days after removal of a thick graft from the abdomen (about 0.034-in. by the dermatome calibration). There is a layer of atrophic epidermis with no formation of rete pegs and absence of hair follicles though sweat glands are present. The newly-formed subepidermic connective tissue has become collagenized, but deep to it are bundles of horizontally-arranged closely-knit collagen fibers. The original dermis can just be made out at the bottom of the photomicrograph. HE × 40 (R.I.S.H. 1476 (2) (42)

although the structural pattern of the dermis has been maintained, yet the physicochemical characters of the collagen have been profoundly altered.

3. *Deep Dermal Burns.*—A thicker layer of dermis is destroyed, exposing the base of the dermis which appears as grossly punctated. Often one may see numerous small islands of epithelium, resembling minute pinch-grafts

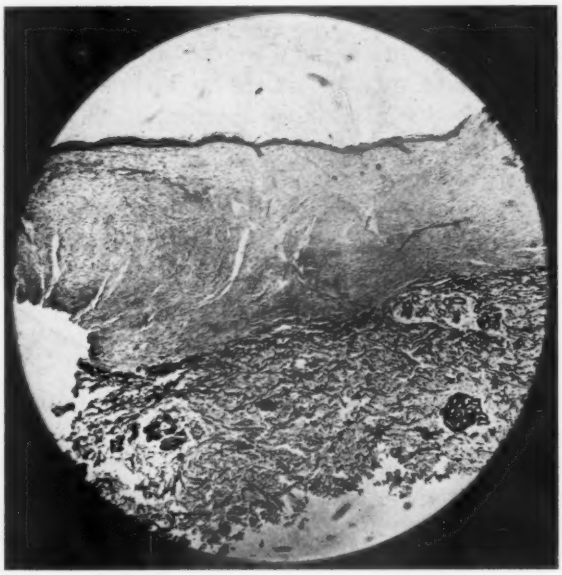


FIG. 19.—Healed hypertrophic-scarred donor area 65 days after removal of a thick graft from the abdomen (about 0.034-in. by the dermatome calibration). The elastica of the original dermis can be seen, but there is virtually no elastica in the newly-formed subepidermic connective tissue or the underlying collagen bundles. Note the thickness of the newly-formed tissue (1.6 mm., 0.066-in.); whereas, in a healed donor area, after removal of a thin graft, the new-formed connective tissue is only 0.36 mm. (0.013-in.) thick. Orcein × 20 (R.I.S.H. 1476 (2) (42). (Compare with Figure 17).

from which epithelization spreads as a pearly-white thin layer. Healing is prolonged, particularly in infected cases. The healed epithelium is often thin, parchment-like and prone to cracking. Histologic examination in the healed stage shows an appearance similar to that described in a healed deep donor area, save that the zone of horizontal collagen fibrils is greater (Figs. 18 and 19).

CONCLUSIONS

SKIN GRAFTING AFTER SUPERFICIAL BURNS

In superficial burns when the deeper layers of the dermis are involved, (deep dermal burns, mixed burns) healing occurs with considerable contraction (inter-island contraction). Although the burn has not caused destruction of the full-thickness of the skin, a loss of skin surface is noted (invisible loss). This contraction and loss of skin surface following superficial burns is noted particularly:

1. When the skin of the area is loosely attached to the underlying structures, *e.g.*, the skin of the dorsum of the hand, or of the eyelids (resulting in ectropion).

2. In the vicinity of joints where it tends to interfere with their normal function.

The newly healed skin is smooth, shiny and very tight; it is often keloidal. Avascular and inelastic scar tissue is the enemy of serviceable repair. Without minimizing the value of massage, ointments and other physical therapy methods, too much time may be wasted in the rehabilitation of patients following superficial burns by their use, particularly in burns of the hands. Roentgenotherapy may be useful to reduce and soften hypertrophic scars, but if scar-epithelium overlies scarred dermis, the best treatment is their complete replacement by thick skin grafts. The presence of a thick dermal pad under the epithelium has been the reason for the serviceable repair given by the split graft.

Skin grafting is indicated in superficial burns for two main reasons:

1. For the relief of skin deficiency, of tightness, following inter-island contraction of deep dermal and mixed burns; particularly on the dorsum of the hand, around joints, for ectropion of the lids or distortion of the features of the face.

2. To replace skin of poor quality. Thin, shiny or keloidal skin is poorly resistant to every day trauma. It tends to crack and ulcerate, even as a result of cold weather. Return of sensation is poor, and the appearance of the skin is often disfiguring.

SUMMARY

1. In the study of superficial burns, a comparative study of 500 donor areas of partial thickness skin grafts were done. The following facts were noted:

1. The quality of the repair was roughly proportional to the rapidity of healing.
2. The rapidity of healing was dependent upon:
   A. The thickness of the graft removed.
   B. The thickness of the skin of the donor site.
   C. The presence or absence of infection.
3. Epithelial healing originates from the epithelial elements in the dermis, hair follicles, sebaceous glands, sweat ducts. The number of these elements decreases in depth of the dermis and so healing is slow.
4. In slow-healing areas, abnormal fibrous tissue is laid down in excessive amounts. The epithelium formed is of poor quality.
5. Contraction following healing is appreciable in areas from which grafts have been cut near the base of the dermis. In deep dermal burns and in mixed burns, such a contraction has been observed and is called "inter-island contraction."

2. From 191 burned patients, 63 biopsy specimens were removed. The extent of the anatomic destruction of the burn wounds and the mode of healing of these wounds were observed.

3. An anatomic classification of burns is proposed.

4. A description of the clinical and pathologic aspects of superficial burns is given.

5. The need for skin grafting certain superficial burns because of the tightness produced as a result of inter-island contraction or because of the poor quality of the healed skin is noted.

REFERENCES

[1] Brown, J. B., and McDowell, F.: ANNALS OF SURGERY, **115**, No. 4, 658, 1942.
[2] Cannon, B., and Cope, O.: ANNALS OF SURGERY, **117**, No. 1, 85, January, 1943.
[3] Brown, J. B.: Int. Abst. Surg., **67**, 105, August, 1938.
[4] Leach, E. H., Peters, R. A., and Rossiter, R. J.: Quart. J. Exp. Physiol., **32**, 67, May, 1943.

BATTLE CASUALTIES IN A SOUTH PACIFIC EVACUATION HOSPITAL

LT. COL. WILLIS J. POTTS, M.C.
UNITED STATES ARMY

WARFARE in the South Pacific involving island to island moves has presented difficult problems in the care of the wounded. Our experience with battle casualties has been far different than we anticipated. Instead of treating fresh wounds, we have had to deal primarily with wounds in which infection was well established upon admission to the hospital. I hasten to comment that this was unavoidable. In spite of a well planned South Pacific surgical program, it was too often impossible to bring wounded soldiers to hospital facilities before the golden six- to eight-hour period following injury had passed. Men were frequently wounded at night and could not be removed from their fox holes before dawn. Then their transportation through jungle and over impassable roads was time-consuming. The best that could be done—and in general it was well done—was to stop hemorrhage, put sulfa drugs in the wounds, apply simple dressings, support fractured extremities with splints and evacuate. This had to be accomplished first by small boat and then by air. The majority of the patients were received at this hospital from two to five days after injury. Some had had further treatment before arriving. The seriously wounded had received blood transfusions but plasma was the mainstay of support in the forward area. In the care and study of these patients a few points of interest presented themselves, and the importance of applying the established fundamental principles of wound treatment was reemphasized.

Gas Gangrene.—In the battle casualties received at this hospital there has been no case of classical gas gangrene. This, of course, may be coincidence, since unquestioned cases of gas gangrene have been reported at other hospitals in this area. Small amounts of air bubbling from an infected wound does not necessarily mean gas gangrene in the ordinarily accepted sense of a death-dealing, spreading infection requiring prompt and heroic treatment. Great caution is advised. We have had five patients with severe wounds, grossly infected, from which gas bubbles exuded and about which slight crackling could be palpated. Because the well-recognized clinical picture of gas gangrene, with severe pain, rapid pulse, relatively low temperature, marked local edema, coppery discoloration of the skin and overwhelming toxicity was absent, we, with considerable trepidation, treated the patients conservatively, in immobilization. Large doses of polyvalent gas gangrene serum were given intravenously. Cultures from the wounds yielded gram-positive, spore-forming anaerobes resembling *Cl. welchii.* Facilities for virulence tests were not available. Since it is well recognized that many patients whose wounds harbor the Welch bacillus do not develop clinical gas gangrene, positive cultures do not warrant amputation or other types

of radical surgery unless the clinical picture supports the laboratory findings. All these patients made an uneventful recovery.

A second group of battle casualties who have air in their tissues, exclusive of chest injuries, and who demand careful differentiation, are those in whom air has been sucked into the tissues by penetrating or perforating missiles. This observation has not been sufficiently stressed in the surgical literature of war. In these patients, clinical examination reveals, to the palpating hand, typical crackling in the tissues but roentgenologic examination shows that collections of air lie along the course of the missile rather than in the planes of the tissues, as in gas gangrene. Furthermore, in the former, the trapped air shows on the roentgenogram as irregular-sized, large and small dark splotches, whereas, in the latter group, the gas is frequently represented by small, dark, oval areas lying in parallel rows.

Our first patient presenting this picture had sustained a wound of his right forearm three days before admission. The shell fragment had entered just above the wrist and, without producing bone injury, had torn through the extensors of the forearm and lodged about one inch above the elbow at the lateral surface of the humerus. His wound was mildly infected at the point of entrance. There was crackling in the tissues all along the course of the shell fragment, and roentgenologic examination revealed blobs of air in the tissue along the tract. The patient did not appear acutely ill; his temperature was 101° F. Because of uncertainty and inexperience, we laid open the tract but found the muscles free from any of the changes so typical of gas gangrene. The wound was packed open with vaselined gauze and a circular plaster encasement applied. Within three weeks, the wound was covered with healthy granulation tissue, allowing a successful secondary closure. We were in error—misguided by the presence of air in the tissues. This condition has been observed and recognized frequently since.

These two groups of patients require most careful and thoughtful observation. Evaluation of air in the tissues of severely wounded extremities or gas formed by microbic action in and about grossly infected wounds is of paramount importance. To delay treatment in the presence of classical gas gangrene is inexcusable—to amputate unnecessarily is tragic.

Infections.—Infection was well established in practically every battle wound when it came under our care. Knife, machete and bayonet wounds, and perforating wounds of soft tissue caused by machine gun bullets were occasionally clean. The extensive wounds were dirty, foul-smelling, and covered with pus and bits of sloughing tissue. Yet, interestingly, there was but one patient in the entire group who had an overwhelming infection, with symptoms of profound toxemia. That is unique because accidental wounds in civilian life are not infrequently followed by severe infections. Cultures from these infected wounds, while unsatisfactory because of the presence of large amounts of sulfanilamide, yielded a variety of organisms—anaerobes, staphylococci, albus and aureus, hemolytic and nonhemolytic, gram-negative bacilli and a few nonhemolytic streptococci. Hemolytic streptococci were

found only once in 25 cases studied bacteriologically. Whether the sulfa drugs in the wounds kill these streptococci or whether the low incidence of upper respiratory infections in this theater of war accounts for the infrequency, is a matter of conjecture. Coincidence may play a rôle. The ironclad rule of wearing caps, sterile gloves and masks covering mouth and nose when treating wounds may be a factor.

The low incidence of infection in potentially clean operative wounds has surprised us, as we were under the impression that wounds would not heal kindly because of the excessive perspiration in the heat and humidity of the tropics. The contrary has been true. In potentially clean operative wounds, we have had infections, with an incidence of two per cent. In 120 consecutive herniae, repaired with silk throughout, there was one post-operative wound infection.

Treatment of Infected Wounds.—The pathology of an infected wound and the physiologic processes involved in its healing have not changed. Often the fundamental principles have been obscured by the host of accepted and discarded lotions, chemicals, salves, washes, irrigants, digestants and wound-healing potions of all kinds. A few make the wounds look better and smell better—that's all. In every infected wound, from a scratch to an extensive avulsion of the muscles of the thigh, there eventually forms, if the patient survives, a barricade between healthy and infected tissue. This wall, or pyogenic membrane, is nature's mechanism of defense against the invasive forces of infection. Anything that enhances its formation is desirable; anything that injures or weakens it is a menace. Each break in that wall, made by instrument or rough handling or "cleaning," is an avenue for bacterial invasion and must be closed by a repetition of the reparative process.

Towards the early, unimpeded and effective building of this wall of defense, all of our energies must be directed. Ever since the Napoleonic wars, astute observers have noted the importance of wound rest, but to Orr rightly goes the credit for popularizing the principles and mechanism of its accomplishment.

Procedure.—An infected, extensive, soft-tissue wound is treated the same as an infected compound fracture, except that in the latter group the fragments are aligned in the best possible position. The mechanism of reduction, alignment and fixation with pins or twin pin units or traction is not within the scope of this paper.

All patients with severe, infected wounds, with or without fracture, are brought to the operating room, where surgical staff and attendants are capped and masked. The dressings are removed with sterile instruments and the wound inspected. The time for débridement has forever passed after infection is established, nor can such a wound be "cleaned" by any process devised by man. Only obviously dead tissue is cut away, and any attempt to cut away live but infected tissue will lead to disaster. If there are pus pockets, they are gently opened. Large foreign bodies, easily available, are lifted out, but during the acute stage of infection there is no digging for missiles

or shell fragments. That can be done after the infection has burned itself out and local as well as general immunity has been established. Washing or sponging, if done, is so gentle that bleeding is not started. The wound is filled, not stuffed, with gauze so thoroughly impregnated with vaseline that it will serve as a nonadherent drain and not as a plug. No rubber drains of any kind are used. A voluminous dressing of fluff-gauze is laid on and about the wound and covered snugly with a liberal amount of sheet wadding. Over this a circular plaster encasement is applied. Because of the excessive humidity in the tropics, it is necessary to make the plaster encasement twice as thick as one would at home.

Wounds of the shoulder and hip are enclosed in plaster spicas; wounds about the knee are protected by leg encasements from groin to toes; wounds about the elbow require encasements from shoulder to fingers. Immobilization is the objective, and it must be complete.

The patient is returned to his ward where his wounds are safe from prying eyes and from fond but meddlesome fingers. Along with rest to the wound and consequent relief from pain come physical and mental relaxation so important in the treatment of any disease. Sulfa drugs by mouth are continued as indicated. Blood and plasma transfusions are used freely as needed.

The patient's temperature will go up as a result of the minor manipulations of a change of dressing and the application of an encasement. A return to normal may be expected within a few days. If the temperature fails to drop in the morning, indicating sealed-up infection, a change of the encasement and a review of the wound is indicated. Excessive drainage and soaking, also, necessitates a change of the encasement. We rarely cut windows in them. If the odor becomes too offensive, the encasement is changed, however, a smelly encasement is largely a matter of mental attitude.

Anesthesia.—Ether administered by the open-drop method is not practical in the tropics because of the high humidity. Practically all cases given ether were induced with nitrous oxide-oxygen and maintained with ether-oxygen administered by the closed absorption technic.

Pentothal sodium, alone or combined with nitrous oxide-oxygen, was found to be the anesthesia of choice for most battle casualties.

Basal anesthesia, consisting of nembutal, morphine and scapolomine, was adequate for many casualties requiring merely a dressing and change of the encasement or minor manipulation of fractures.

Spinal anesthesia was not used for battle casualties. Other methods were considered safer.

Based on these experiences, there are a few "do's" and "don'ts" that are very elemental but seem to require constant reiteration:

1. Record, record, record.
2. Especially in case of upper extremity injuries: Is the radial pulse present, are the nerves intact, are the tendons severed? Make a record.
3. Do not close battle wounds.

4. Dry gauze packed in wounds acts as a plug—use only when absolutely necessary for control of hemorrhage.
5. Immobilize adequately. Do not use unpadded encasements on patients who are to be removed from your own continuous personal observation.
6. Do not use rubber drains—never in the region of large vessels. Gauze, *thoroughly* impregnated with vaseline, properly placed, will allow for adequate drainage. Do not pull strips of vaselined gauze through perforating wounds.
7. Roentgenograms and records are frequently lost or do not accompany the patient, therefore, with indelible pencil, write on the encasement: Date of injury; date of application; draw position of fragments in all fractures; indicate wound of entrance and wound of exit with a circle the size of the wound and write in the circle, "vaselined gauze."

CONCLUSIONS

Our results with this simple regimen have been: Patients who eat well, sleep well and are happy because they are free from pain. Their wounds clean themselves without interference and become covered rapidly with healthy granulation tissue.

URINARY COMPLICATIONS OF PELVIC ENDOMETRIOSIS

J. R. GOODALL, M.D.

MONTREAL, CANADA

SECONDARY ENDOMETRIOSIS of the urinary organs is a relatively unusual complication, although the condition has been recognized for some years. The urinary tract may be invaded in any part of its length below the junction of the middle and lower third of the ureters. The disease may be localized to any single part of this tract or it may, by progressive advance, involve all the structures below the brim of the pelvis. In the cases herewith cited are (1) two instances of diffuse stromatous secondary endometriosis, involving the whole urinary tract below the brim of the pelvis, causing occlusion of both ureters and leading to complete destruction of the kidneys and death, owing to uremic coma; (2) there are also two other instances of secondary invasion of a single ureter by transperitoneal penetration, leading to destruction of the kidney on that side; and (3) one instance of secondary urethral endometriosis.

The symptomatology varies considerably in different cases due to several factors: (1) The site of the urinary implantation; (2) the cellular structure from which the disease originated; which (3) determines whether the endometriosis present in the urinary tract responds to the monthly cycle or not. These main factors will be emphasized in their appropriate sections.

In the author's monograph, "A Study of Endometriosis," it was emphasized that all cases of endometriosis originate in the endometrium. The endometrium is made up of two specific cellular structures—the stromal cell and the lining cell of the uterine secretory glands. Endometrial ectopias may be made up wholly of (1) the stromal cells, simulating sarcomatous disease which are, therefore, designated as stromatous endometriosis; or (2) the ectopias may be composed of glands and stroma and, therefore, may be termed mixed endometriosis. It was further emphasized that only the superficial layers of the endometrium respond to the monthly cycle, whereas, the deeper layers are not appreciably affected. For this reason, endometrial cells from the superficial layers may retain their capacity for cyclical response when they implant in ectopic position, whereas, the deeper, nonresponsive cells are resistant to monthly cyclical influences when in ectopic position.

It can readily be seen that there are three modes of invasion of the urinary tract by endometrial tissue: (1) Direct, by lymphatic continuity or back-flow from the deep uterine mucosa through the uterine wall into the muscularis and mucosa of the bladder; (2) indirect, from implants in the peritoneal vesico-uterine pouch and thence into the muscularis and mucosa of the bladder; and (3) traumatic displacement, with implantation on the peritoneal surface of the bladder following surgical intervention in any case of endometriosis. From these sources of transmission it follows that Group I

invasions affect chiefly the trigone and base of the bladder, where there is direct lymphatic continuity with the uterus, while Group II and III invasions affect chiefly the fundus of the bladder. It is to be noted that the endometrial tissue in Group I cases arises from the deep uterine mucosa and is not responsive to the uterine cycle. The same is not true of the endometrial tissue aggregates in Groups II and III. These are chiefly instances of peritoneal implants or traumatic transplants resulting from "spill" and are primarily derived from the responsive superficial portion of the endometrium. These factors determine the presence or absence of the chief diagnostic sign due to endometriosis of the urinary tract, namely, cyclic urinary hemorrhage.

SECONDARY URETHRAL ENDOMETRIOSIS

To the best of my knowledge there are no recorded cases of secondary urethral endometriosis. One case came under my observation some seven years ago.

Case Report.—The patient complained of burning on micturition, but no frequency or other discomfort. On examination, there was a growth about the size of a white bean protruding from the orifice of the urethra. She said that it became larger at times, and appeared inflamed, and a small amount of pinkish discharge was noted. She could not determine that there was any increase at the time of menstruation because of the vaginal flow, but the growth did seem more troublesome and larger during this cycle. Not knowing its character, I did not urge immediate surgical intervention, because it was assumed that it was an innocuous urethral caruncle. Four days after her first visit her husband stated that she was suffering intense discomfort in that region, and that he was taking her to the hospital. On examination, it was found that the growth had increased to five or six times its previous dimensions, and that a diffuse thrombosis had occurred. She was menstruating at the time. The mass was now a dark purple in color, it filled the urethra, and protruded about three-quarters of its bulk outside. Removal by cautery was done, and the biopsy revealed typical endometrial tissue, which was much distorted by interstitial hemorrhages, dilated blood vessels and thromboses. Recovery was uneventful.

The patient was 38 years of age, and, though married 16 years had never conceived. Examination of the vagina and pelvis at the time revealed nothing suggestive of pelvic endometriosis except a few hard nodules in the rectovaginal septum near the posterior vault, which, I think, undoubtedly, in view of the biopsy findings, must be looked upon as previously unrecognized endometriosis. Roentgenotherapy was instituted, and the patient did not have any further complications.

Two other cases were described in the author's monograph, "A Study of Endometriosis." In these cases the entire length of the urethra was involved but since in each case this was merely a part of a diffuse pelvic infiltration, description will be deferred.

SECONDARY INVOLVEMENT OF THE BLADDER WALL

The first recorded case of bladder endometriosis was that by Judd, in 1921, entitled "Adenomyoma Presenting as a Tumor of the Bladder." Two cases by Floyd Keen, reported in 1925, were entitled "Perforating Ovarian Cysts (Sampson's), with Invasion of the Bladder Wall." Then appeared Whitehouse's report, in 1926, of "Endometriosis Invading the Bladder of a Woman

who had never Menstruated." After a lapse of several years there followed a series of cases by Sauer, in 1932; Weijtlandt, in 1934, Phillips, in 1934; Perlmann, in 1934; Henriksen, in 1935; Mark, in 1937; McClelland, in 1938; and Adams, in 1938. The description of the picture varies considerably in many of these cases, as does, also, the symptomatology, but no adequate explanation was forthcoming to account for these discrepancies. The symptoms vary with the type of the disease and the location of the growth. Frequency and urgency usually are the first symptoms to draw attention to the bladder. In over 30 per cent of the reported cases there was a previous record of pelvic operation for intraperitoneal endometriosis. Usually, when the bladder involvement is a direct progression of the disease from the uterine parietes, there is no hematuria, and the bladder invasion may be felt in the anterior fornix in the region of the uterovesical contact. In the invasion of the bladder by a secondary transplant from the peritoneum, the pathologic process is preponderantly in the fundus of the bladder and is responsive to the menstrual cycle. Periodic hematuria, in relation to the cycle, is the *most important diagnostic sign* of the disease. This sign is present in only a small percentage of cases, however, for the reasons given above. In a careful review of the reported cases, the transplants of endometriosis to the bladder from an intraperitoneal endometriosis followed surgical pelvic intervention in the majority of cases. Spontaneous involvement in the vesico-uterine pouch by intraperitoneal endometriosis, occurs in only about one per cent, as compared with 100 per cent of involvement in the pouch of Douglas. From this, it will be seen that surgical intervention and opening of the vesico-uterine pouch in cases of intraperitoneal endometriosis, is a strong predisposing factor in the incidence of secondary bladder endometriosis.

Cases of bladder involvement fall into three groups: Group I.—Cases of stromatous endometriosis. Group II.—Cases of mixed endometriosis derived from the deep layer of the endometrium by lymphatic extension through the uterine parietes. Group III.—Cases of involvement of the fundus of the bladder from peritoneal endometriosis.

Group I.—In this group are two cases of stromatous endometriosis which, as described in "A Study of Endometriosis," invaded all of the pelvic structures, resembled a sarcoma, and the invasion of the bladder wall was just a part of the general involvement by contiguity. In both these cases, the bladder muscularis, including its sphincteric muscle, lost its contractile function due to replacement fibrosis. Incontinence ensued, followed by an acute fetid cystitis. The mucosa never became appreciably involved and, consequently, there were no vesical symptoms or signs until cystitis developed. The ureters were affected also, as were all the pelvic structures, and this resulted in occlusion of the ureters and destruction of the kidneys.

Group II.—In this group we find those cases of bladder involvement in which the endometriosis, made up of glands and stroma, has originated from the deep layers of the uterine mucosa and, after traversing the uterine lymphatics, invaded the bladder muscularis at the point of attachment of the

bladder to the uterus. This invasion is nonresponsive to the menstrual cycle, and, when examined cystoscopically, one sees a growth, with widespread edema, and, when the submucosa is involved, there appear pearly-white cystic growths of various sizes, from millet seeds to that of a bean. The growth is preponderantly in the region of the base of the bladder, frequently involving the trigone and interureteral space. There is no rhythmic hematuria, but there may be microscopic blood at times.

GROUP III.—In this group are those cases of involvement of the bladder by transplant from a source of preëxisting intraperitoneal endometriosis. Thirty per cent of these cases have followed pelvic operations, and, in the majority of these, the bladder was injured surgically by separation during an hysterectomy. As most of such cases are derived from intraperitoneal disease, which, in turn, is derived, in the great majority of cases, from a tubal "spill," these are responsive to the menstrual cycle, and rhythmic hematuria becomes the most efficient diagnostic sign of bladder endometriosis. The cystoscopic picture varies with the time of the examination; during the interval of two menstrual periods, there is a bladder growth, surrounded by edema, congestion and blue grape-like cystic masses. Hematuria is slight, but during the menstrual period the edema and congestion are very marked and hemorrhage is fairly abundant from most of the surface. The growths are preponderantly in the fundus when there has not been any surgical trauma, but where the normal bladder relations may have been disturbed, the growth may invade any part of the surgically exposed bladder surface.

SECONDARY URETERAL ENDOMETRIOSIS

Primary involvement of the ureter in endometrial disease is an exceedingly rare condition. A single case is reported by Randall. By primary involvement it is meant that the ureter was the primary urinary structure showing demonstrable disease. It does *not* mean that the disease arose primarily in the ureter. I repeat, all cases of endometriosis, according to my thesis, are of endometrial origin. Randall's case is of interest. It is entitled "Endometrioma of the Ureter."

Case Report.—Miss C. K., white, age 37, complained of right-sided pain, frequency, nocturia and hematuria. She developed these symptoms in August, 1940. In November, 1940, she had a severe attack with hematuria. She had gained weight recently. There was no cyclical bleeding. Physical examination revealed nothing abnormal except tenderness in the costovertebral angle. Uranalysis was negative except for a few leukocytes, and many red blood cells.

An intravenous urogram showed the left genito-urinary tract to be normal. On the right there was haziness of the shadow of the kidney, pelvis, infundibula and calices. The right ureter showed multiple filling defects. *Clinical Diagnoses:* Generalized lesion involving the pelvis, infundibula and right ureter. Possible ureteritis cystica or multiple polypi of the right ureter.

A cystoscopic examination showed a normal bladder. After a retrograde pyelogram, the diagnosis was made of a mural growth in the distal end of the right ureter. Neoplasm was to be excluded.

Operation.—December, 1940: Through a Gibson incision into the right retroperi-

toneal space, the ureter was freed almost to the bladder. A fusiform swelling was located about 3 cm. proximal to the bladder. At this point, the ureter was found to be firmly attached to the peritoneum. The ureter was cut near the bladder and the kidney removed. Biopsy revealed typical endometrial tissue. During the operation, the peritoneal cavity was opened, and the pelvis was explored by the finger. No pelvic or abdominal pathology was encountered.

There are four cases of ureteral disease in my series. The first two cases were recorded in the Transactions of the Association of American Gynaecological, Obstetrical and Abdominal Surgeons; and last year they appeared in greater detail in the author's monograph, "A Study of Endometriosis."

These two cases were instances of stromatous endometriosis, in which the patients lived for 11 and 12 years, respectively, after the first operation, at which the disease was discovered. The two cases were so similar in all their details, that one description will cover most of the salient symptoms and pathology.

Cases 1 and 2.—Both were women, ages 38 and 36 years, respectively. Both were operated upon for what was considered uterine fibroids. At operation, a diffuse uterine stromatous endometriosis was found. In the first patient, the disease had extended up the lymphatics of the right broad ligament into the right iliac fossa, where a diffuse growth had developed. In the second patient, the left broad ligament was invaded. Subtotal hysterectomy was performed. The reason for not undertaking a more extensive operation, was because the disease, at the time, had only been recently recognized, and there was no doubt that, clinically, we were dealing with a diffused uterine sarcoma, which had spread beyond the limits of the uterine wall, and was beyond extirpation.

The patients were treated with full doses of roentgen ray, and one of them with radium. Recurrences developed in each case and there were alternating periods of growth and recession, these corresponding to intervals during which irradiation therapy was or was not employed. Eventually, after ten years in one case, and 11 years in the other, the growth became roentgen ray-fast and no longer responded appreciably. From then on, there was a slow, relentless invasive process, which involved the walls of the rectum, bladder, vagina, and urethra. Both cases were very similar in their clinical course. The rectum and vagina became almost leaden in hardness, and the urethra became so tortuous that catheterization was impossible. Incontinence, both rectal and vesical, developed, followed by a fetid cystitis; hematuria developed, and the patients were constantly wet. This condition continued for two or more years. Eventually, nausea and vomiting supervened, and the patients sank into uremic coma. Blood chemistry showed marked retention of products of metabolism, and death followed in due course.

At autopsy, in the one case, the bladder and urethra were found to be invaded on all sides by new growth, but the mucosa was not broken through at any point. The hematuria was chiefly, if not wholly, the result of the cystitis. The ureteral walls were invaded in their lower two-thirds by the same endometriotic new growth, and though nowhere was the lumen invaded, the caliber had been impenetrably reduced by encroachment from the walls. The ureters above the constriction, were dilated and the kidneys were reduced to two small sacs with walls about one-third-inch thick. This slow degeneration of the kidneys had been progressive, evidently over years. Roentgenograms taken of the whole body while on the autopsy table, revealed no metastatic growths, but, though the lungs seemed perfectly normal, to the eye and touch, yet, microscopically, small miliary nodules were found to have permeated the pulmonary tissues—apparently, the sequela of a broken-down nodule in the internal iliac vein. Autopsy could not be obtained in the second case, but the course of the disease was parallel to the first.

Prior to her death, she began to show signs of mental aberration, followed by vomiting, and she gradually sank into an uremia coma.

There were no other cases until quite recently. In both of the following cases, the ureters were involved as a complication of intraperitoneal endometriosis. In neither of these cases was the bladder involved, and the chief symptom was costovertebral pain on the affected side.

Case 3.—The first patient was a young woman, age 28, who had suffered for many years with pain in the right lower abdominal quadrant, which was diagnosed as appendicitis. Appendicectomy was performed but the pelvis was not examined through the McBurney incision. Microscopic study showed that the appendiceal mucosa was normal, but that the external surface of the organ was invaded by endometriotic growth. Her condition was not improved by the appendicectomy. Her pain in the right lower quadrant grew gradually worse and was now referred also to the right loin. When examined by the author, a choked pelvis was found, in which the right side was more involved than the left. She had been married eight years, but had never become pregnant. She had severe dysmenorrhea both premenstrual and menstrual in character. For several years right-sided backache was the chief symptom. Six months before coming under observation, she had episodes of exacerbation of the backache, and, she thought, some fever during these periods. Catheter specimen of urine revealed pus, and blood in small quantities. These symptoms were not at all rhythmic and, hence, did not suggest any association with menstruation.

At operation, the pelvis was a mass of endometrial blood cysts, and dense adhesions. The sex organs were released with great difficulty, especially on the right side, where the subperitoneal tissues, after liberation of the ovary, showed a deep infiltration by the growth. The bladder was normal to palpation, but through the extensive incision, the right ureter was found dilated above the pelvic brim, and the right kidney was reduced to a small sphere not much larger than a golf ball. The left kidney was larger than normal, due to compensatory growth. Three years have elapsed since the operation. Her period of febrile exacerbation and urinary symptoms continued for over a year, with longer intervals of freedom and diminution of the symptoms. For the past six months, she has been quite free from discomfort, and it is assumed that complete sequestration of the kidney has developed.

Case 4.—The second patient was an unmarried female, age 43; of delicate structure, fair and anemic. She complained that during the past four years, she had suffered from a feeling of stiffness in her back on the left side, and, during the same period, had had repeated attacks of pain in the right lower quadrant. She had had lassitude for the past four years, but this symptom became very pronounced during the last six months. She stated that she had no pain on voiding, occasional frequency, and hematuria for one week about three weeks ago. Her periods were regular, at 25-day intervals, lasting five days, without dysmenorrhea or leukorrhea. Her urine constantly showed about 40 to 50 red blood cells (h. p. f.), and from 10 to 25 pus cells, with occasional faint traces of albumin. Every one of the 34 specimens examined showed myriads of bacteria.

She was a patient of Doctor McCaffrey's and, due to her hematuria, Doctor Seng, an urologist, was called in consultation. His first cystoscopic report, September 16, 1943, was as follows: ". . . . Bladder mucosa normal; no tumor or foreign body seen. On the trigone, there is a mild pseudomembranous trigonitis with scattered yellowish-brown cysts, about the size of a match head. There are only three or four of these. Right ureteral orifice identified and right ureter catheterized. Specimen obtained.

"The region of the left ureteral opening was edematous and, as the ureteral orifice could not be identified, the ureter was, therefore, not catheterized.

"The specimen from the right kidney (about 75 cc.) was cloudy. Red blood cells about 25–30 (h. p. f.).

"Roentgenograms showed the right catheter to the renal pelvis where it was looped in the pelvis; no evidence of calculus; left renal region obscured by gas. Right retrograde pyelogram, with 4 cc. of 12 per cent sodium iodide, showed a small pelvis of bifid type. Kidney in good position. Left kidney still obscured by gas.

"In view of the fact that we were unable to identify the left orifice, owing to the edema about it, an intravenous urogram is indicated."

Cultures from the right kidney were negative. Blood chemistry showed urea 13.2 mg. per 100 cc.; urea nitrogen 6.2 mg. per 100 cc.; uric acid 2.5 mg. per 100 cc.; creatinine 1.14 mg. per 100 cc.; and N. P. N. 15 mg. per 100 cc.

September 17, 1943: Intravenous urogram: At five minutes—much gas in intestines obscures both kidney regions but dye can be seen excreted in the bladder; at 15 minutes—dye can be seen in right renal pelvis, and the lower right ureter is clearly outlined—normal. It is not clear whether the left kidney is excreting or not. There is much gas in the region. Later, no outline of left kidney visible. At 30 minutes—no definite outline of left kidney. *Urologic Opinion:* The question of a functioning left kidney not settled. A second urogram suggests a possible left hydro-ureter and left ureterocele.

September 24, 1943: Cystoscopic examination under spinal anesthesia: The bladder mucosa as previously reported. The region of the left ureteral opening was pouting; no orifice distinguished. This area was congested. Attempts to pass the catheter up the ureter not successful. The three small yellowish cysts in the trigone (previously reported) were congested also.

Vaginal Examination.—A large right cystic mass and a smaller one on the left, apparently without relation to the ureteral disease on that side. (Doctor Seng). There was a sudden rise of temperature, with chills, after the last treatment. Symptoms and signs disappeared five to seven days later.

When first seen by the author, September 22, 1943, a small asymmetrical uterus, with solid masses in both lower quadrants, was found. These were more or less symmetrical and there was a possibility, among other things, that this might be a Krukenberg tumor, because the patient had suffered for a long time from gastro-intestinal symptoms. Accordingly, a gastro-intestinal series was taken, with negative results. Wassermann was negative.

Operation.—October 12, 1943: The upper abdomen was found to be free from adhesions. There were signs of old blood, and blood pigment, about the sigmoid and coils of the small intestine. The pelvis was filled with adhesions, involving both appendages, but chiefly the left, which were bound down densely to the sigmoid, mesorectum and parietal peritoneum posteriorly. The left ovary contained a large "chocolate" cyst the size of a tangerine. The right appendages were liberated with ease. But the left with extreme difficulty. During the process of liberation, the cyst ruptured and its adherent walls had to be peeled off by forceps and traction. Both appendages were removed, followed by a subtotal hysterectomy. The appendix, short and rigid, was also removed. Exploration of the renal regions disclosed a dilated left ureter, and a kidney reduced to about one-half normal size, globular, fixed, and giving the sensation of a small thin-walled sac, filled with fluid. The right kidney was about one-third larger than a normal kidney.

The patient made a smooth recovery for five days, but owing to an error in orders, the house surgeon removed both the skin clips and the stay-sutures, and immediately afterwards, the patient sneezed violently, which was followed by vomiting and a severe pain in the region of the incision. Inspection showed that the wound had opened in the middle third and that the intestine was protruding. The tissues were clean, and the incision was immediately closed by through-and-through sutures. Her recovery was smooth and uneventful.

DISCUSSION.—These four cases divide themselves into two distinct groups. The first two were cases of stromatous endometriosis, of a diffuse nature, arising from the stromal cells of the endometrium, and spreading to invade all the organs of the pelvis, with a slow destruction of their normal functions. Thus, we saw the rectum and bladder completely lose their muscular resilience and the development of consequent incontinence. The vagina became a rigid canal through the same cause. Infection spread up the urethra and bladder and a double pyonephrosis followed upon a slow constriction of the ureters by the new growth, with complete destruction of the kidneys, and death, owing to uremic coma. In these cases, the invasion was wholly by the lymphatics, and completely extraperitoneal. The ureteral canals were never invaded, but merely obstructed by irregular nodular invasions of the ureteral walls. In cross-section of the ureters, in places the ureteral lumen was semilunar, due to a growth on one side only. In other places the constriction was annular. The constriction in both these cases finally became bilateral, but probably not synchronously so. In the two other cases, the ureters were constricted by an endometriosis of, primarily, intraperitoneal "spill," with subsequent subperitoneal involvement of one ureter, so that destruction of the corresponding kidney became an inevitable sequela.

I have consulted Doctor Seng, and other urologists, as to the fate of these two last cases, and there is a uniformity of opinion, that one of two things will eventuate: (1) Either the affected kidney will completely atrophy and cause no subsequent trouble; or (2) a large pyonephrotic sac may develop that may require removal. The first of the two cases reported, has now gone over two years, and her general health seems to be steadily improving. The other was operated upon four months ago. Doctor McCaffery informs me that she has had kidney "flare-ups," but that these are growing less severe and less frequent. It will be noted that in neither of these two cases was the ureteral disease complicated by endometriosis of the bladder.

An effort has been made in the literature to classify bladder endometriosis as primary or secondary. This subdivision I cannot endorse, because I have tried to demonstrate that all cases of endometriosis of whatever type, or in whatever pelvic site, are endometrial in origin. Henriksen states that his case of vesico-uterine endometriosis was of primary vesical origin. He states: "I feel that the term 'primary vesical endometriosis,' should be limited to those cases in which no demonstrable contiguity with uterus, fallopian tubes or ovaries is present, and in which there has been no surgical trauma of the bladder wall or its peritoneal reflection." That is not a very convincing argument. One might as well contend, then, that all tumor metastases in the liver are primary because there is no continuity with the primary growth. By the same token, Krukenberg tumor of the ovaries would be primary ovarian cancer, and many other examples could be added to prove the falsity of such a contention.

Ernest Mark's statements *apropos* to this subject, are of significant interest: "The case reported by Whitehouse . . . received no surgery. There was

no involvement of the mucosa. This case, like that of Henriksen, did not have cystoscopy prior to operation, and the endometriosis arose from tubal and ovarian involvement in the ectopic process and involved all the serous and muscular coats of the bladder. It is my opinion that this case, and others of like character, should not be included under the heading of bladder endometriosis and, most certainly, cannot be termed endometrioma of the bladder." May I add, parenthetically, that the term "bladder" in these cases, as outlined in my study, should be used in such cases merely as a regional denomination, and not in a sense of primary origin of the disease.

In my series, the first two cases were ones of stromatous endometriosis, in which the ureters were involved late in the disease—to be more specific, ten, or more, years after the disease was discovered. The ureters were just part of a general invasive disease involving all the pelvic structures, with eventual destruction of the kidneys, and death owing to uremic coma. In these cases, the bladder, though extensively involved as to its musculature, maintained its retentive power until the sphincter became involved, and incontinence developed; following this, acute fetid cystitis developed, and ultimately double pyelitis followed. In the two other cases the disease was not parametrial from the uterine parietes as in the former two, but was of the "spill" character, through the fallopian tubes, and the ureter in each case became involved in its pelvic course, by transperitoneal invasion. The bladder was not involved in either case, except by local edema at the corresponding ureteral orifice, due to lymphatic block.

In these two cases, the outstanding symptoms were, therefore, not vesical in origin, but resulted from the diseased kidney, and frequency and urgency were conspicuous by their absence before urologic intervention.

These two cases, I think, are the first to be reported of transperitoneal ureteral stricture without previous involvement of some layer of the bladder. In the cases of involvement of the bladder mucosa, the triad of symptoms—frequency, dysuria, and hematuria—are fairly constant. In only a small percentage of cases, can the hematuria be shown to synchronize with the menstrual cycle. When this is present, the diagnosis is much facilitated.

Symptoms.—From what has gone before, it is quite evident that the symptoms of endometriosis depend upon several factors: (1) The part of the urinary tract affected; (2) the type, and, therefore, the origin of the endometriotic transplant.

The case of urethral endometriosis was indistinguishable, on inspection, from an ordinary urethral polypus.

In bladder endometriosis, it is commonly asserted that the three fairly constant symptoms are frequency, urgency and hematuria. Hematuria is frequently only microscopic in cases where the new growth is chiefly muscular, and the mucosa merely shows signs of lymphatic and vascular obstruction. In cases of transperitoneal involvement of the bladder mucosa, the bladder disease is usually responsive to the menstrual rhythm and the hemorrhages are, therefore, accentuated rhythmically.

Visually, through the cystoscope, there is usually a tumor, with marked edema, and in the nonresponsive cases the cysts, if visible, are of a pearly opalescence; but in the responsive type, the cysts are of a dark blue grape-like color, with fairly profuse hemorrhage from these during menstruation. In the two reported cases of stromatous endometriosis of the bladder, the chief symptoms arose out of lack of contractility of the bladder and sphincter musculature, followed by incontinence and cystitis. In the two cases of ureteral obstruction there were no outstanding vesical symptoms, but severe costo-vertebral pain forced these patients to seek relief. In these cases, there was destruction of the kidney on the side of the obstructed ureter. The other kidney had hypertrophied compensatorily. In the two cases, where both ureters were blocked, the patients died of uremic coma, consequent upon the destruction of both kidneys.

Treatment.—The treatment resolves itself into the same as that for endometriosis elsewhere in the pelvis. I cannot see the rationale, or the efficacy, of excision of the bladder tumor when the agency which brought about the bladder involvement is still left in operation.

REFERENCES

Adams, P. S.: Jour. Urol., **40**, 390, 1938.

Baker, W. G., and Brewer, J. I.: Trans. Amer. Assoc. G. U. Surgeons, **34**, 135, 1941.

Goodall, J. R.: A Study of Endometriosis. Lippincott, 1943.

Henriksen, Ekle: Primary Endometriosis of Bladder. J. A. M. A., **104**, 1401–1403, 1935.

Judd, E. Starr: Adenomyoma Presenting as a Tumor of the Bladder. Surg. Clin. North America, **1**, 1271–8, 1921.

Keene, Floyd E.: Perforating Ovarian Cysts, with Invasion of the Bladder Wall: Report of Two Cases. Amer. Jour. Obst. and Gynec., **10**, 619, 1925.

McClelland, J. C.: Trans. Amer. Assoc. G. U. Surgeons, **31**, 215, 1938.

Mark, Ernest G.: Jour. of Urology, **37**, 799, 1937.

Perlman, Simon: Endometriosis of Bladder. Urol. and Cutan. Rev., **38**, 700–703, 1934.

Phillips, Richard B.: Endometriosis Vesical. Jour. Obst. and Gynec., Brit. Emp., **41**, No. 2, 165, 1934.

Randall, Alexander: Jour. of Urology, **46**, 419, 1941.

von Sauer, H.: Endometriosis of Urinary Bladder. Zentralbl. f. Gynäk., **57**, 347–350, 1932.

Weijtlandt, J. A.: Endometriosis of Bladder. Proc. Roy. Soc. Med., **27**, 1493, 1934.

Whitehouse, H. B.: Endometrioma Invading Bladder Removed from a Patient who had never Menstruated. Proc. Roy. Soc. Med., **19**, 15, 1925.

AN APPLICATION OF STAGING IN THE REMOVAL OF DIFFICULT WILMS' TUMORS

EVERETT D. SUGARBAKER, M.D.

COLUMBIA, MO.

FROM THE SURGICAL SERVICE OF THE ELLIS FISCHEL STATE CANCER HOSPITAL, COLUMBIA, MO.

IT IS NOW WELL RECOGNIZED that there exists a group of renal neoplasms of mixed cellular components which, although they may occur from fetal life up to late adult life, are most frequently found in infancy and early childhood, where they make up approximately one-fourth of all tumors seen. They are characterized by rapid growth to bulky size, metastasize particularly to the liver and lungs, and have a quickly fatal termination. The relative absence rather than the presence of symptoms is striking in view of the marked physical findings. The earliest report of such an entity was written by Gairdner,[6] who, in 1828, described a case of "fungus haematodes of the kidneys." The clinical setting and postmortem findings in his patient were typical, although bilateral involvement was present. Eberth[4] in 1872, was the first to present a microscopic description of the process. In 1894, Birch-Hirshfeld[3] first used the term embryonal adenosarcoma, since designated by Ewing[5] as embryonal adenomyosarcoma. Wilms,[16] in 1899, thoroughly reviewed and clarified the subject in a monograph titled "Mixed Tumors of the Kidney," and the eponym "Wilms' tumor" is now generally accepted. The term renal embryoma, although less specific in its connotation, has, also, through frequent usage come to be identified with these neoplasms.

The proper method of treating Wilms' tumors has been the subject of a good deal of discussion. The usually marked, and occasionally phenomenal, regression in size produced by external irradiation has led to widespread use of this form of therapy. That fully viable-appearing tumor remains after heavy dosage has been shown by Bothe,[1] and is reflected in the uniformly poor results following the use of roentgenotherapy, either when used alone or as a preoperative adjunct.

The results following surgery alone, however, as reported by Mixter,[14] and Ladd and White,[9] have, by comparison, been so far superior to those, that one must accept that primary nephrectomy undertaken without delay is unequivocally the best method of treatment at the present time and should be promptly carried out whenever possible. There seems little doubt but that their results were due to two main factors: the saving of very valuable time in dealing with an acute neoplasm by omitting preoperative roentgenotherapy, and the employment of a transperitoneal approach. Much stress has been placed by Ladd on the primary ligation of the renal pedicle before the major portion of the tumor is disturbed, in order to prevent the possible dissemination of tumor emboli incident to manipulation. Recently, McDonald and Priestley[12] have demonstrated renal vein involvement in 45 per cent of

31 Wilms' tumors studied, so that initial pedicle ligation would appear to be of more than theoretic importance.

A second important advantage of the abdominal approach, heretofore not mentioned but certainly just as important as the care of the hilus, is the ability provided for excising the kidney in its anatomic envelope—Gerota's fascia. The renal capsule is normally not a very substantial covering (Fig. 1) and, as a result of the stretching produced by the tumor, it may become extremely thin (Fig. 2). Surrounding the capsule is the perinephric fat, which is usually diminished in amount or absent around the embryomas. Surrounding this, in turn, and completely enveloping the kidney is the renal fascia, first described by Gerota,[7] in 1895.

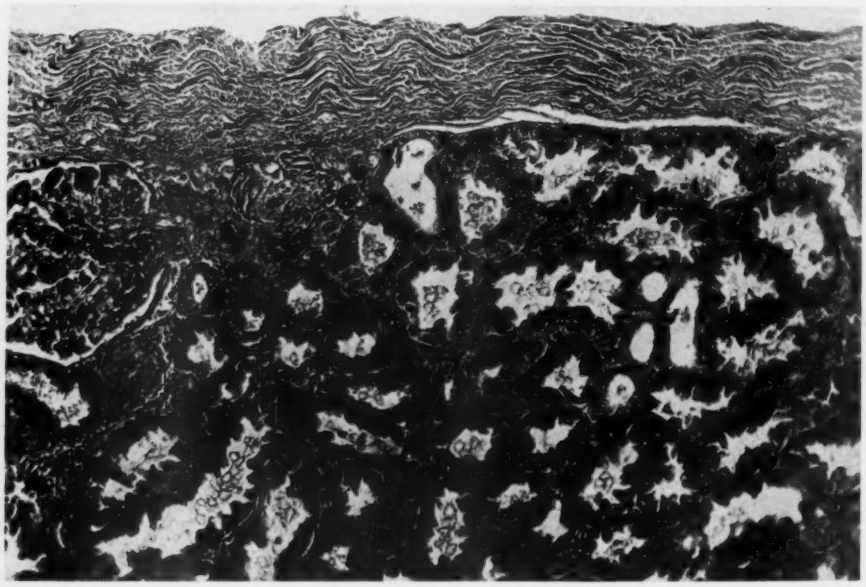
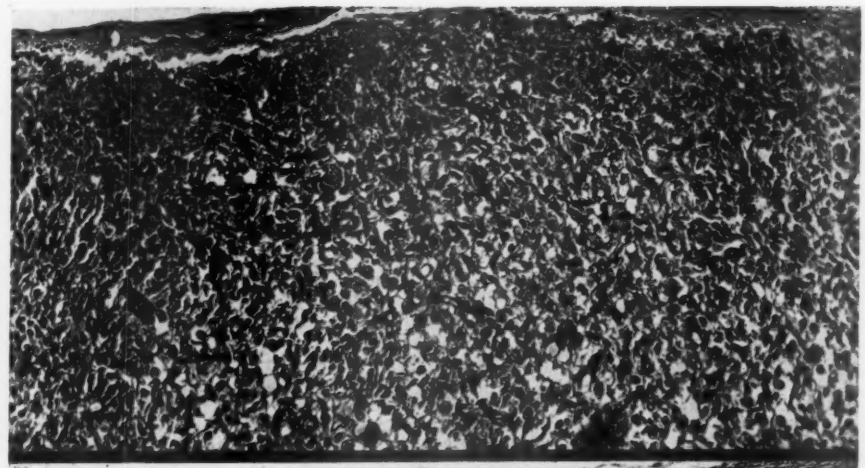


FIG. 1.—Normal kidney with capsule attached, to indicate its thickness relative to underlying structures.

Gerota's fascia, synonymously referred to as Gerota's capsule, renal fascia, perirenal fascia, fascia propria, and tunica fibrosa, arises from the transversalis fascia as a short band which splits into two layers to invest the kidney and the perirenal fat in a fairly thick posterior layer (fascia of Zuckerkandl), and a somewhat thinner anterior layer (fascia of Toldt). By some anatomists (Davies,[2] and others) these are looked upon as concentrations of a more peripheral portion of the sub- or extraperitoneal fascia. There is general agreement, among those who have so carefully worked out the anatomy of this capsule, that the posterior layer attaches to the bodies of the vetebrae in front of the psoas muscle. The precise disposition of the anterior layer has been the subject of some dispute. Gerota originally described it as crossing the midline anterior to the renal and neighboring great vessels and continuing as the corresponding layer of the opposite side. Southam[15] was able to trace

FIG. 2



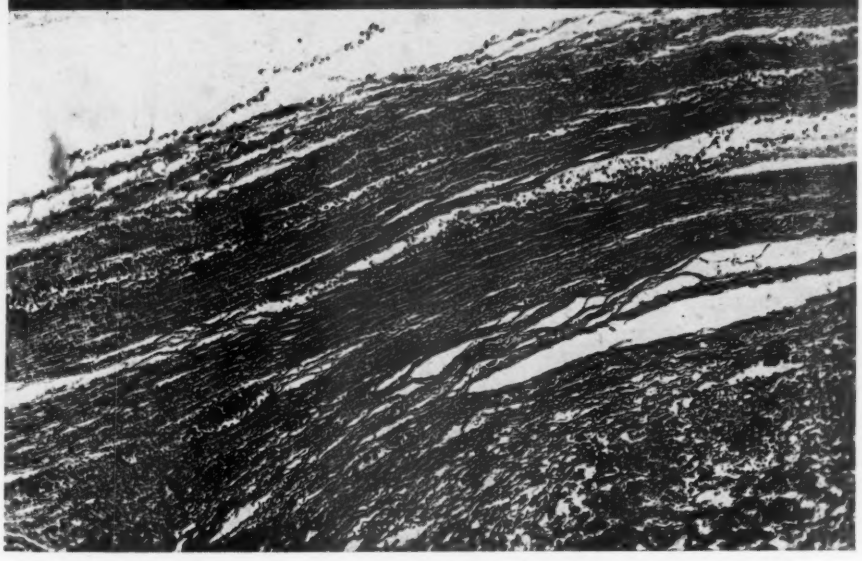


FIG. 3

FIG. 2.—Marked thinning-out of capsule over bulky Wilms' tumor. In many areas (not shown) capsule is only one cell thick. (Section from case presented)

FIG. 3.—From another case of Wilms' tumor, indicating infiltration of renal capsule and renal fascia by tumor cells. As anticipated, recurrence in the tumor bed developed shortly following nephrectomy.

the fascia anteriorly only as far as the pancreas and the root of the mesentery. Considerable support was added to Southam's work by Mitchell[13] who, after injecting an emulsion of barium into the perinephric space, took radiographs and noted strict localization of the barium to the side injected. Spread across the midline occurred only after a considerable amount of the material had been injected and, then, at the level of the lower lumbar vertebrae. Quite recently, the problem has been clarified by Martin,[11] who traced the anterior layer across the midline from one side to the other, but found that both the anterior and posterior layers split on the medial aspect of the kidney to completely surround it and there are pierced by the hilar vessels (Fig. 4).

At the upper pole of the kidney both the anterior and posterior layer of fascia fuse with that on the undersurface of the diaphragm. At the lower pole

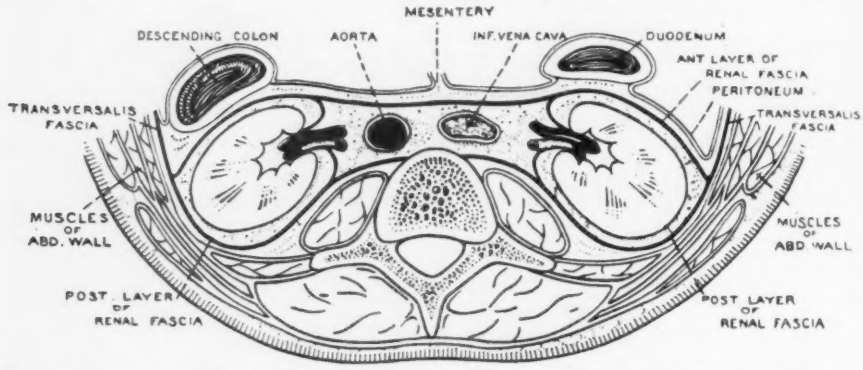


FIG. 4.—Transverse section showing arrangement of renal fascia. (From Cunningham's Anatomy, 8th Edit., pp. 1464).

of the kidney they do not blend, but invest the ureter and gradually fade out as they are traced downward (Fig. 5).

Surrounding the perirenal fascia posteriorly, lying chiefly between it and the parietal musculature, is the paranephric fat often referred to as the fatty capsule of the kidney. This is present in lesser amount anteriorly between the same fascia and overlying viscera and is a derivative of the subperitoneal fascia. This latter structure in its typical fibro-areolar form covers the kidney only where the kidney lies immediately beneath the peritoneum.

In removing the renal fascia with the kidney, therefore, the fascia must be divided above, below, and mesial to that organ. Its incision mesially is necessary in order to approach the hilar vessels. The removal of Gerota's fascia through a lumbar approach would be difficult, and it is doubtful whether it could ever be done neatly or in its entirety under any but exceptional conditions. Usually, in lumbar nephrectomies, this fascia is entered posterolateral to the kidney from which it is completely stripped in order to secure the hilar structures. With most embryomas, such a procedure would be almost certain to result in future recurrence.

The operability in Wilms' tumors, as with most tumors, will depend largely on the skill and experience of the surgeon. Mixter,[14] in 30 cases,

reported an operability of 73 per cent. Apart from metastases, the factors responsible for the operative rejection of most cases have been local. This is emphasized by the numerous statements in the literature advocating preoperative roentgenotherapy as a means of diminishing the size of the tumor and, thereby, facilitating surgery. Since the difference in end-results between

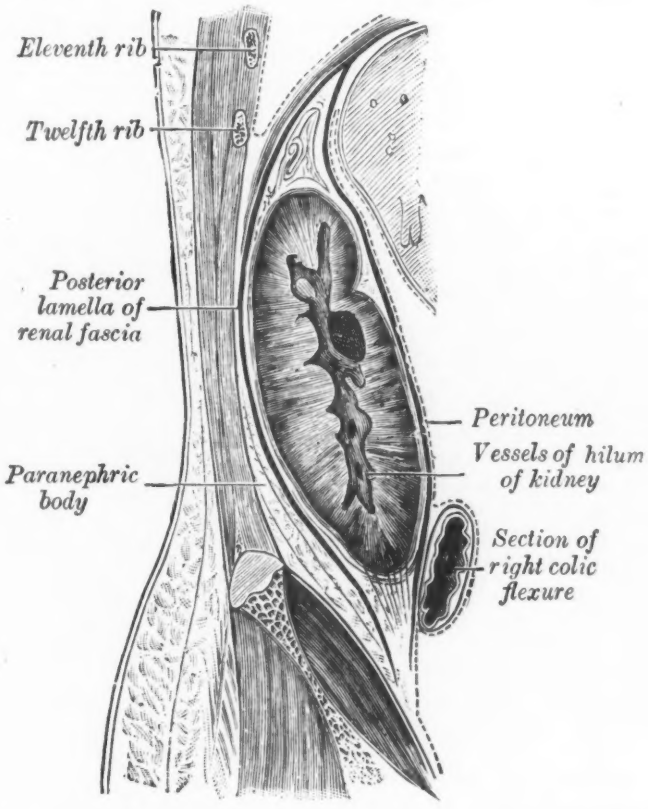


FIG. 5.—Disposition of renal capsule as seen in sagittal section through the posterior abdominal wall. (From Gray's Anatomy, 22nd Edit. pp. 1212).

the preoperatively irradiated and the primarily operated patients now points to the danger of the first mentioned course, there appears to be excellent reason for attempting to extend the operability by dividing the operative procedure up into stages, if necessary, in order to carry out the prompt removal of the tumor with minimum risk. There are two main technical difficulties involved: first, the handling of the pedicle and, second, the control of the bleeding in freeing the kidney. In bulky tumors, considerable distortion of the normal anatomy takes place. The colon, duodenum, pancreas, spleen, *etc.*, are usually considerably displaced, along with their blood supply. Usually, the mass completely overlies its pedicle, making approach to the vessels difficult. This, added to the possibility of marked shortening of the renal veins or adherence of the mass to, or actual invasion of, the wall of the vena cava,

may convert what was intended to be the preliminary to a nephrectomy into a time-consuming, hazardous procedure in itself. Another difficulty frequently encountered is vigorous bleeding from the markedly dilated and thinned-out perinephric veins. The danger, here, arises less from blood loss than from interference with exposure and the dependent uncertainty of dissection.

A case presenting these difficulties is, herewith, described, and demonstrates a workable method of staging. It is probable that several variations of such a procedure are possible, but the anatomy of the kidney as well as the natural tendencies of Wilms' tumors, suggest that the procedure here followed will be found to be the one most frequently useful.

CASE SUMMARY

Case Report.—Hosp. No. 3719: C. A., a 12-year-old boy, was admitted to the hospital, January 16, 1942. His parents stated that in October, 1941, after an appendicectomy, an abdominal mass had been noticed which had been increasing rapidly in size. Intermittent hematuria had been present, and back pain had been prominent. According to the referring physician, no mass had been found at previous celiotomy.

Examination showed a bulky, rubbery mass extending from beneath the right costal margin to the symphysis pubis. It occupied the entire right abdomen and extended beyond the midline to fill almost half of the left abdomen from the umbilicus laterally.

Uranalysis was negative; no red cells were present. Blood examination revealed an hemoglobin of 10 Gm. per cent (70 per cent), and R. B. C. of 3.9 million; and a W. B. C. of 11,550, with 78 per cent granulocytes. The N. P. N. was 18.6 mg. per cent.

A roentgenogram of the chest showed no metastases, and an intravenous pyelogram indicated a nonfunctioning right kidney.

First-Stage Operation.—January 23, 1942: The abdomen was entered through a large right-sided T-shaped incision. The tumor had displaced the liver anteriorly. The right colon lay in the left side of the abdomen. The stretched parietal peritoneum, lateral to the ascending colon, was incised and bluntly stripped off the left side of the mass in an attempt to approach the renal pedicle. No right lateral mobility could be obtained, however, because of marked adherence of the left renal vein to the posterior aspect of the tumor. Only a single left renal vein could be identified, but it was nevertheless divided. The vena cava could then be seen lying in a groove on the midposterior aspect of the mass with which it communicated in two places. The communications represented the original right renal veins, two in number, which as a result of the expansion of the tumor had become so shortened and broadened that no pedicle any longer remained and a direct entry of blood from tumor into the vena cava had been established. Each of these flattened structures measured about 5 cm. in breadth, the upper one also encompassing the left renal vein orifice in its scope. With the vena cava controlled by circular tapes above and below the mass, a longitudinal segment of the wall of the vena cava, corresponding to the entry of the upper of these two veins, was removed and the lumen closed using a continuous interlocking suture of fine silk. The right renal artery supplying the mass was next divided. At this point, the patient appeared to be having considerable respiratory embarrassment and it was reported that the blood pressure had been slowly but steadily dropping despite continuous blood replacement. A great deal remained to be done but it was feared that any prolonged hypotension might too seriously interfere with the function of the right kidney. The procedure was terminated, therefore, with the expectation of completing the removal at a later time.

Postoperatively, the child did very well. Repeated examinations of the left testicle

failed to demonstrate any swelling and the daily N. P. N. never rose higher than 28.3 mg. per cent.

Second-Stage Operation.—January 29, 1942 (six days later): The abdomen was reopened, and in less than ten minutes dissection was being continued from the point which it had taken three and one-half hours to reach in the first stage. Moreover, the capsular veins which had been tremendously dilated and thin-walled at the first stage now were thrombosed, making dissection not only easier but much more precise.

Tapes were again placed around the vena cava and the lower venous connection between it and the tumor was severed by removing a similar longitudinal segment from

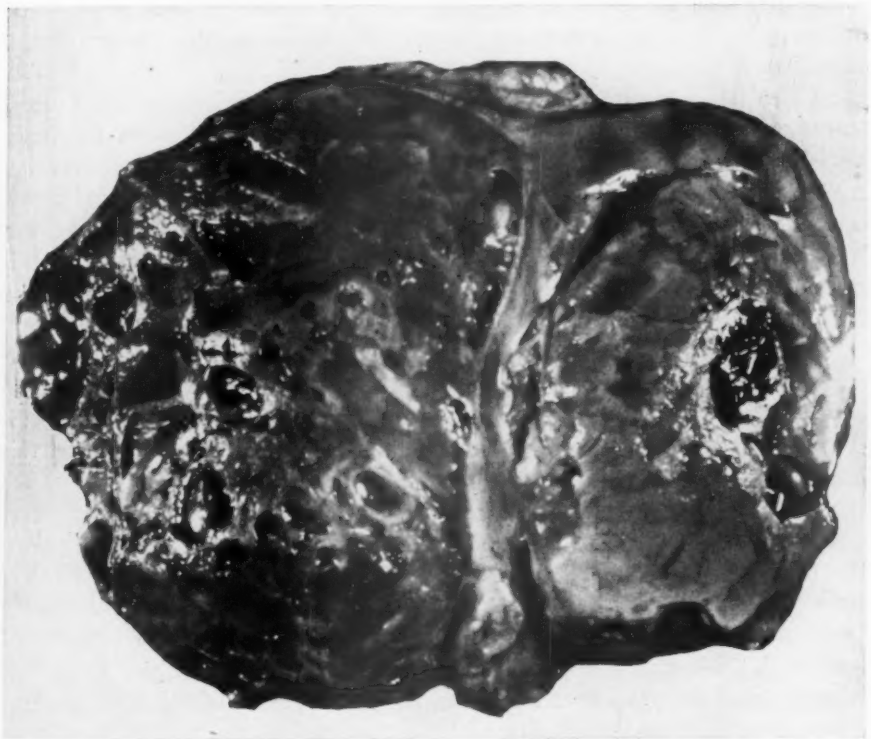


FIG. 6.—Cut-surface of tumor in case presented. Shows numerous cystic spaces and thinned-out zone of normal kidney (2/3 actual size).

the vena cava. This second opening was closed in an identical manner as was the first one. The tumor appeared to be quite adherent to the diaphragm, and in carrying out sharp dissection the tumor was entered, with resulting spillage. The area of adherent diaphragm was extrapleurally excised. Sharp drops in blood pressure occurred during these manipulations. The parietal peritoneum was resutured, a flank drain was placed, and the abdomen closed.

The tumor weighed 1,760 Gm. (Fig. 6). It had a fairly dense connective tissue capsule in most places, but in some areas this was extremely thin. On microscopic examination, the typical appearance of Wilms' tumor was present. There was no vein involvement observed.

The postoperative course was uneventful. Between February 12 and March 6, 1942, 2,000 roentgens (measured in air) was given to each of two 15- x 20-cm. fields, one anterior and one posterior. Other factors were 200 KV, 15 ma., 50 cm. T. S. D.,

and 1 mm. cu. and 1 mm. al. filter. This produced some erythema of the skin, but no moist reaction.

Follow-up has now continued more than two years, and the child has remained well, and is developing normally.

COMMENT.—Although some form of a rectus incision may be employed satisfactorily in removing smaller tumors, a large T-shaped incision would seem to be more useful in the removal of the larger ones. The horizontal limb must often extend from costal margin to pubis, with a vertical limb extending laterally at the level of the umbilicus well into the flank. The advantage of this lies in enabling the surgeon to roll the tumor laterally with a minimum of squeezing to gain access to the pedicle.

Often the colon and, to a lesser extent, the more medially situated structures are displaced anteriorly and medially by the expansion of the mass. This often leaves a wide stretch of peritoneum between the lateral border of the colon and the abdominal wall. This peritoneum and its own underlying fascia are unnecessary for subsequent closure and may, therefore, be left on the tumor. Moreover, since the anterior layer of the renal fascia is thinner than the posterior layer, the removal with the kidney of the peritoneum and subperitoneal fascia presents an added safeguard against tumor recurrence.

Complications, such as tumor adherence to, or definite invasion by tumor of, segments of the inferior vena cava, the projection of large thrombi from the renal vein into it, or the conversion of the renal veins into renal sinusoids by distortion and shortening incident to tumor growth (as occurred in this case) are more apt to occur on the right than on the left side because of the shorter length of the right renal vein (or veins).

Small to moderate defects left in the vena cava by longitudinally excising portions of its wall may be closed by suturing with a continuous over-and-over or interlocking black silk suture. In repairing after large excisions the lumen may occasionally become so narrowed as to partially obstruct the return flow of blood. When this occurs, so much bleeding may result at the suture line that ligating the vena cava may become necessary. This happened recently in a case of carcinoma of the kidney. It is now well known that ligature above the entry of the left renal vein is almost invariably fatal but that ligature below that vessel is usually followed by the development of a good collateral circulation.[17] Since the necessity for this procedure usually occurs during surgery on the right kidney, the location and identity of the left renal vein must be positively established before any ligating of the vena cava is done.

It is interesting to note that in the case presented here, a right nephrectomy and a ligation of the left renal vein were simultaneously accomplished without subsequent untoward results. Multiple renal veins on either side are common, but both at the time of ligation and at the second stage of the procedure, attempts to find another left renal vein in this case were unsuccessful. It must, therefore, be assumed that sufficient collateral circulation of the left kidney was immediately established to maintain a normal N. P. N. post-operatively. The collateral renal venous return may take place by way of

the left spermatic, renal capsular and the adrenal and azygos systems. The renal capsular vessels have established communications with the phrenic, portal, ureteral, and spermatic veins. Lejars[8, 10] was able to demonstrate renal-azygos communication in 80 per cent of cadavers he examined. It is easy to appreciate that the situation here is in no way analogous to ligating the inferior vena cava above the left kidney since the factor of caval back pressure is absent in the case presented.

Occasionally, very marked tortuous dilatation of the capsular veins is seen in kidney tumors. After the hilar vessels have been ligated and several days are permitted to elapse, these vessels are either considerably diminished in caliber or have become thrombosed. Dissection of the tumor capsule may then be carried out accurately without the handicap of profuse bleeding which may intermittently obscure the field.

In several recent cases, capsular vein engorgement was associated with extensive invasion of the renal veins by tumor. In one of these a single right renal vein was completely occluded by a sausage-like tumor thrombus. It is possible that the surgeon may be able to predict major involvement of the kidney veins at the operating table with considerable accuracy.

Over 90 per cent of the surgically-treated Wilms' tumors that are not cured will recur or metastasize during the first year following operation. It is extremely rare for the disease to reappear after the second year. The case presented has now gone two and one-half years since operation, and therefore, may be reasonably expected to remain well.

SUMMARY

1. The proper treatment of Wilms' tumors is discussed: The results indicate that preoperative roentgenotherapy does considerable harm by delaying nephrectomy. Local postoperative irradiation should probably be administered following specific indication (not empirically) and a more careful attempt made at evaluating its results.

2. In view of the high incidence of local recurrence following the removal of renal embryomas, more attention should be paid to the advantages to be derived from a clearer idea of Gerota's fascia.

3. It seems likely that if preoperative roentgenotherapy is to be discarded as an aid to surgery, and if a high operability and low mortality are to be maintained, certain cases will have to be staged.

4. Such a case is presented because it demonstrates so well the difficulties which may be encountered and what may be accomplishd to overcome them.

REFERENCES

[1] Bothe, A. E.: Tissue Changes in Mixed Tumors of the Kidney After Roentgen Irradiation. J. Urol., **33**, 434–442, May, 1935.

[2] Davies, J. W.: Abdominal and Pelvic Fascias: With Surgical Applications. Surg., Gynec. and Obst., **54**, 495–504.

[3] Döderlein, A., and von Birch-Hirshfeld, F. V.: Embryonale Drüsengeschwulst der Neirengegend im Kindesalter. Centralb f. d. Krankh. d. Harn u Sex-Org., **3**, 461–488, 1894.

[4] Eberth, C. J.: Myoma Sarcomatodes Renum. Virchows Arch. f. Path. Anat., **55**, 518–520, 1872.
[5] Ewing, J.: Neoplastic Diseases. W. B. Saunders Co., Philadelphia, 1940.
[6] Gairdner, E.: Case of Fungus Hematodes in the Kidneys. Edinburgh Med. and Surg. J., **29**, 312–315, 1828.
[7] Gerota, D.: Beitrage zur Kenntniss des Befestungsapparates der Niere. Arch f. Anat. u Entwickl., pp. 265–282, 1895. (Verlag Von Veit and Comp., Leipzig.)
[8] Hyman, A., and Leiter, H. E.: Surgery of the Inferior Vena Cava in Urologic Conditions. J. Urol., **45**, 813–826, June, 1941.
[9] Ladd, W. E., and White, R. R.: Embryoma of the Kidney (Wilms' Tumor). J.A.M.A., **117**, 1858–1863, November 29, 1941.
[10] Lejars: Taken from Hyman and Leiter.[8]
[11] Martin, C. P.: A Note on the Renal Fascia. J. Anat., **77**, (pt. 1), 101–103, October, 1942.
[12] McDonald, J. R., and Priestley, J. T.: Malignant Tumor of the Kidney. Surg., Gynec. and Obst., **77**, 295–306, September, 1943.
[13] Mitchell, G. A. G.: The Spread of Retroperitoneal Effusions Arising in the Renal Regions. Brit. Med. J., **2**, 1134–1136, December 9, 1939.
[14] Mixter, C. G.: Malignant Tumors in Infancy and Childhood. ANNALS OF SURGERY, **96**, 1017–1027, July, 1932.
[15] Southam, A. H.: The Fixation of the Kidney. Quart. J. Med., **16**, 283–308, July, 1923.
[16] Wilms, M.: Die Mischgeschwülste der Niere. Leipzig, Arthur Georgi, **1**, 1–90, 1899.
[17] Wittenberger, J. L., and Huggins, C.: Ligation of the Inferior Vena Cava. Arch. Surg., **41**, 1334–1343, December, 1940.

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EXTERNAL PIN TRANSFIXION OF FRACTURES

AN ANALYSIS OF EIGHTY CASES

IRWIN E. SIRIS, M.D.

NEW YORK, N. Y.

FROM THE DEPARTMENT OF SURGERY, NEW YORK UNIVERSITY COLLEGE OF MEDICINE AND THE NEW YORK UNIVERSITY SURGICAL DIVISION, BELLEVUE HOSPITAL, NEW YORK CITY, N. Y.

THE INTEREST MANIFESTED in the use of external pin fixation has prompted us to report the results of our experiences with 80 cases treated during the past three and one-half years on the New York University Division of Bellevue Hospital.

Roger Anderson, Haynes, Stader and many other advocates of external mechanical pin fixation of fractures have endeavored to facilitate the management of fractures by painstaking inventions and creations of refinements in their instruments and technic.

At first glance, one is overwhelmed by the ingenious contrivances, which seem so mechanically intriguing. One becomes further impressed when the patient is ambulatory and demonstrates some mobility of his joints.

However, in our experience, the high incidence of discharge around the pin sites alone, would be sufficient reason to preclude the use of the method as a routine procedure (Table I). Nevertheless, this method of treatment

TABLE I

INCIDENCE OF DISCHARGE FROM THE PIN SITES

			Discharge from Pin Sites		Osteomyelitis Pin Site			
	No. of Cases	Per Cent	No. of Cases	Per Cent	No. of Cases	Per Cent	Sepsis	Died
Humerus:								
Simple.....	4	5%	3	75%	No			
Compound.....	1	1%	..	.....	No			
Ulna:								
Infected.....	1	1%	1	100%	1	100%		
Tibia and fibula:								
Simple.....	31	38%	10	32%	10	32%		
Compound....:	23	28%	6	26%	4	17%	1*	1*
Neck of femur...:	7	8%	7	100%	..	.....	5	5
Femur:								
Simple.....	12	15%	9	75%	3	33.3%	1†	1†
Compound....:	1	1%	1	100%	..	.....	1‡	1‡
Total.....	80	100%	37	46%	18	22.5%	8	8

* Died on 75th day of cerebral thrombosis, pneumonia, cirrhosis of liver and sepsis.

† Died on 2nd day, 103 years old—Russell traction for 19 days; restless and unmanageable; then pin fixation.

‡ Died on 36th day from multiple injuries.

should not be entirely discredited. Many of the infections around the pin sites may have been averted by laying less stress on ambulation and mobilization of joints, by immediately immobilizing the extremity and pins in plaster and by applying a new encasement when the swelling subsided. Our high

mortality in hip fractures may have been prevented by employing internal instead of external pin fixation. We have not been able to obtain the excellent results which the proponents claim for the "castless" external pin fixation for fractures of the hip. In our opinion it should not be used for fractures of the hip.

Nevertheless, external mechanical pin fixation with plaster is useful if restricted to certain problem fractures in which conservative treatment will not give a satisfactory clinical result.

While it is not the purpose of this paper to analyze and discuss the various forms of mechanical pin fixation and the principles and methods of the procedures employed, we cannot refrain from calling attention to some of the fundamental principles evolved as a result of the use of the methods by the proponents and by our own experience.

I—PRINCIPLES IN THE APPLICATION OF EXTERNAL PIN FIXATION

1. Meticulous surgical technic.

2. Knowledge of basic anatomic and mechanical factors in reposition of fragments.

3. Simultaneous skeletal traction, countertraction, rigidity of the pins and of the fragments.

4. The pins should be rigid and large and have no elasticity or spring.

5. Sustained impaction or contact.

6. Avoidance of sustained distraction.

7. Avoidance of encroachment of the pins on (1) major neurovascular structures; (2) capsule; and (3) articular surfaces.

8. Use of two or more pins in each major fragment if feasible; one pin in a fragment does not prevent shearing, rotation or redisplacement.

9. (a) Half pins should penetrate the opposite cortex to assure stability and firm leverage.
   (b) The points of the half pins should not project beyond the opposite cortex into muscles, and cause irritation and inflammation.
   (c) Half pins should preferably be inserted on the medial side of the tibial fragments where the bone is devoid of muscles.

10. (a) When using half pins converging angular insertion of the pins to the transverse and longitudinal diameter of the fragment, engages a larger cross-section of bone and assures better control during manipulation of the transfixion connecting rods and for immobilization.
   (b) To facilitate traction other than by the use of an anatomical splint, the distal through-and-through pin, inserted at right angles to the long axis of the shaft at the site of election, permits utilization of the distal pin for more effective direct traction.
   (c) "The Haynes self-tapping pin is a combination drill, tap and pin in one unit. The drill is the proper size for the root diameter of the tap which enables the tap to cut a clean thread in the cortex and

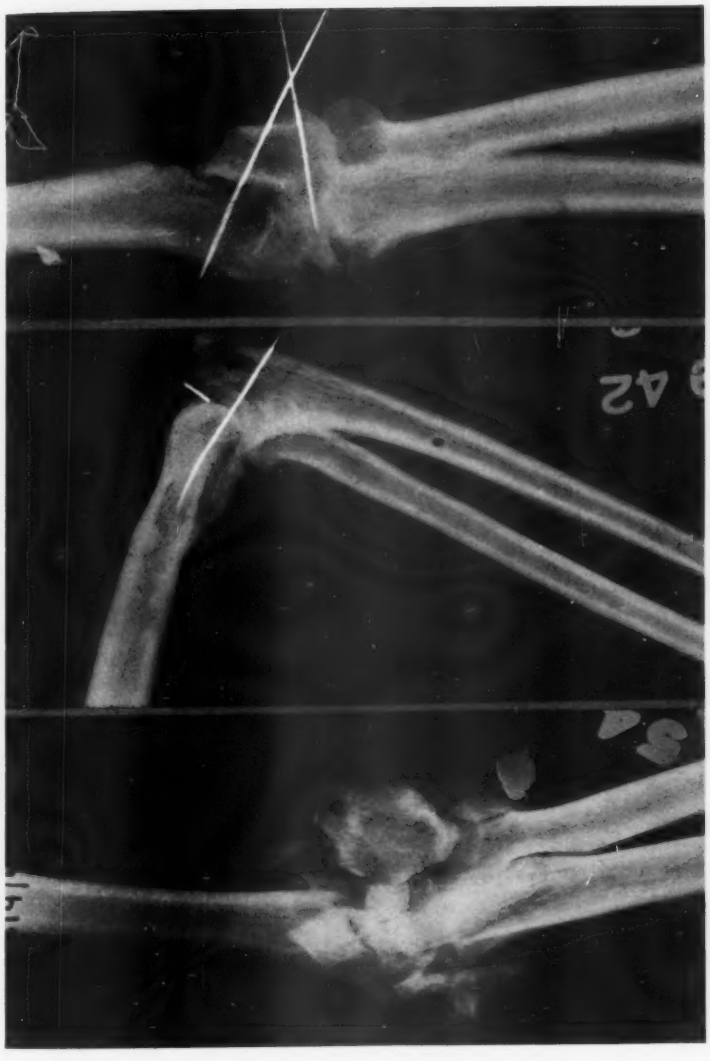


FIG. 1a FIG. 1b FIG. 1c

FIG. 1.—a. Compound comminuted fracture lower end of humerus—May 4, 1942.
b-c. Anteroposterior and lateral view after reposition of fragments using a Van Gorder exposure and transfixing pins.

in continuing to turn the pin you have a full thread in the cortex with the drill point anchored in the opposite cortex. The thread is intended to prevent the pin from coming out and should not create pressure to cause necrosis. The Haynes pins are inserted at right angles (1) because it is easier to insert; (2) the pressure line is the center of the bone and it would be more rigid than if inserted at an angle; and (3) the greater the angle the greater the load the pin has to carry."

11. (a) *Plaster of paris incorporating the pins and adjacent joints is indispensable in the use of external pin fixation in simple fractures* of the tibia and fibula, and in some simple fractures of the femur. It is absolutely *imperative* for *compound* fractures.

(b) With evidence of diminished swelling and movement in plaster, the connecting rods should be refastened and a new encasement applied to prevent friction of the soft tissues against the pins and to more rigidly immobilize the fragments.

12. If there is no loss of bony structure and *plaster is employed,* the pins should be *extracted within three to five weeks in tibial* fractures and *within five to seven weeks in femur fractures.* Before extracting the pins determine if the encasement fits snugly; if not, fix the pins and the connecting rods, change the anterior or posterior shell or the entire encasement and check roentgenographically.

Joints—Comminuted Fractures.—External transfixion with strong Kirschner wires by closed or open reduction and immobilization of the transfixion pins and adjacent joints in skin snug-fitting plaster encasement is desirable where distal skeletal traction is not feasible or fails to realign comminuted fragments. This procedure is particularly applicable to extensive comminuted simple and compound fractures of the elbow. The Van Gorder incision for exposure of the articular surfaces is especially desirable as the fragments can be visually fitted on to the Kirschner wires which are inserted through the intact skin over either condyle. A plaster jacket, with an anterior and posterior moulded plaster of paris splints, with circular turns, is applied to the arm with pyramids of plaster fixing the protruding wires. The pins are extracted in four to six weeks (Fig. 1—a, b, c, d and e).

In simple or compound comminuted fractures of the astragalus, a similar procedure is advocated. The anterior or posterior shell of plaster should be changed alternately when the swelling subsides.

II — PROCEDURE OF REDUCTION FOR SIMPLE AND COMPOUND FRACTURES

Where a Roger Anderson reduction splint is available, the use of the self-aligning splint will greatly facilitate reduction. The anatomical splint, or chassis, is not absolutely necessary to effect reduction (Fig. 2). Traction, manipulation and reduction can be obtained on an ordinary traction table. This is facilitated by inserting the basic traction pin in the most suitable site for the most effective traction.

Fractures of the Femur.—A strong Steinman nail is inserted just above the adductor tubercle. The desired number of pins are then inserted at the sites of election (Figs. 3—a, b; 4—a, b; and 5—a, b). Slight traction is exerted through the distal pin and fixed to the traction table with the knee flexed as much as the location of the fracture would demand. Rotation is corrected by manipulating the pin rods and, almost simultaneously, the extra

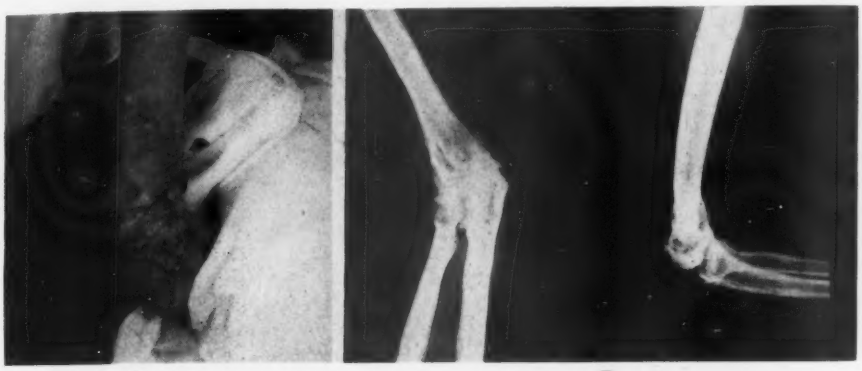


FIG. 1d FIG. 1e

FIG. 1.—d. Encasement removed, site of skin graft. Pin extraction June 30, 1942.
e. January 6, 1944—range of mobility 60°–80°.

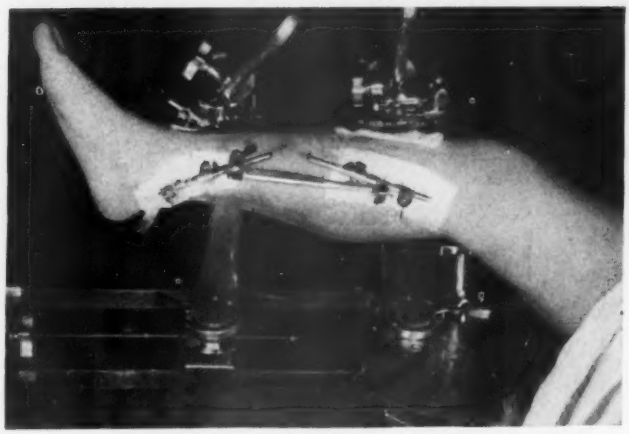


FIG. 2.—Roger Anderson reduction splint used for a fracture of the tibia and fibula; through-and-through pins; fracture units joined with connecting rods. Plaster slabs around pin sites.

traction is applied in the direction of the long axis of the fragments. After the fragments are manipulated into position, the rods connecting the dual, triple or quadruple pins are clamped to the long connecting fixation rod, or rods, to maintain the fragments in position. After verifying the corrected position of the fragments roentgenologically a double plaster spica is applied which also incorporates the pins.

Fractures of the Tibia and Fibula.—A Boehler Braun splint; a Boehler traction frame; a traction or an ordinary operating table may be used. The

Boehler traction frame or traction table is especially desirable if the fracture is compound as the wound is more readily accessible for débridement. Traction may be effected through the os calcis if the fracture is in close proximity to the ankle. More effective traction and reduction is facilitated if the distal pin can be inserted through the tibia, preferably two finger's breadth above the internal malleolus. The desired pins are then inserted into the fragments (Fig. 6). The short connecting rods are attached to their pins

FIG. 3a

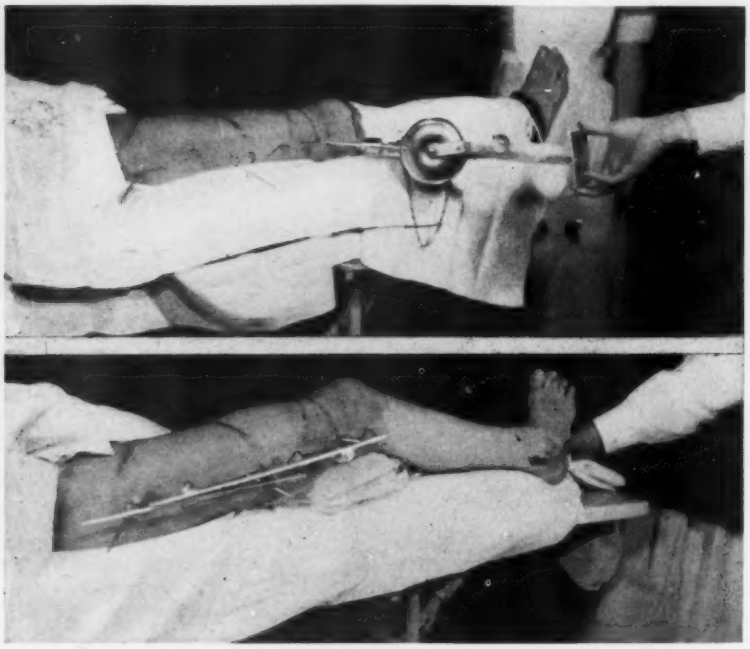


FIG. 3b

FIG. 3.—a. On ordinary operating table, lines indicating desired sites of insertion of half pins.
b. Half pins inserted, intermediate connecting rod connected to fracture units.

and the fragments are manipulated into position. The two units of dual, triple or quadruple pins and their connecting rods are fixed to each other by one or more connecting rods. A moulded anterior, posterior and circular plaster encasement incorporating the pins is applied from the toes to the groin with the knee in 30° flexion.

Humeral Fractures.—The two half pins in the proximal fragment are inserted slightly anteriorly and laterally so as to converge obliquely backward. The two half pins in the distal fragment are inserted posteriorly so as to converge obliquely forward. The short connecting rods are attached to their pins. The right-angled flexed elbow and the midpronated forearm is then fixed on a traction table with bandages over felt. Or a Kirschner wire may be inserted one inch below the olecranon process and fixed to the adjustable

traction arm. The fragments are then manipulated into position. The long connecting rod is clamped to the fracture units. A plaster spica is then applied.

Forearm Fractures.—Depending on the location and the direction of the displacement of the proximal fragments, the flexed forearm is placed in a

FIG. 4a

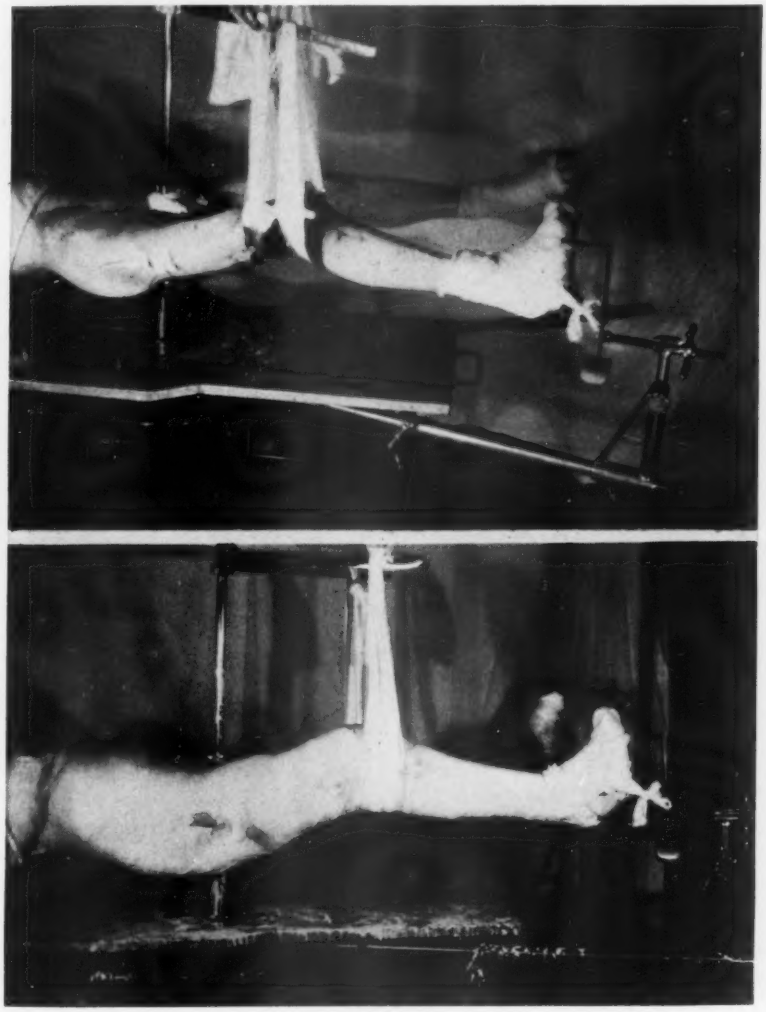


FIG. 4b

FIG. 4.—a. Hawley table—through-and-through and half pins inserted.
b. Plaster spica incorporating projecting pins.

position of supination, midpronation, or complete pronation. A pin is then inserted through the radius and ulna, two finger's breadth above the tip of the styloid process. Where the fracture is in close proximity to the wrist, the hand is placed in complete pronation with the four fingers in extreme

adduction. A Kirschner wire is then inserted through the second metacarpal bone at the base of the web between the thumb and index finger. The pin should penetrate at least two metacarpal bones. The pin is connected to a caliper and a rope which extends over a pulley on the traction ex-

FIG. 5a

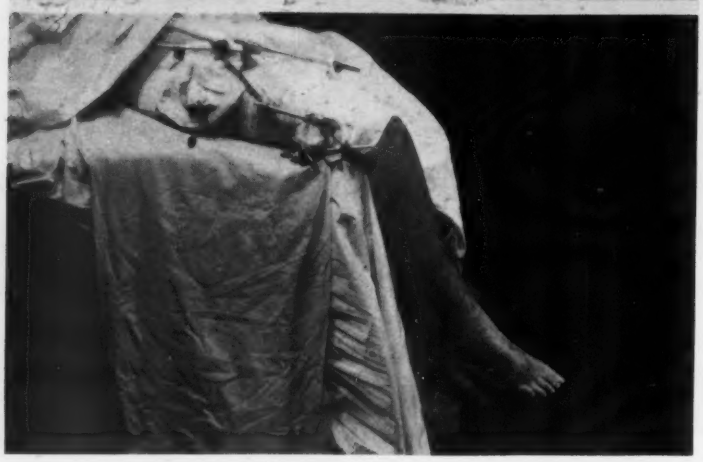


FIG. 5b

FIG. 5.—a. Reduction and fixation of a fractured femur with aid of anatomical splint.
b. Rods connected to fracture units.

tension frame with five to ten pounds traction. The weight of the arm is usually sufficient for countertraction. If necessary the arm, just proximal to the flexed elbow, can be fixed to the frame with a sling over a piece of felt. When the desired position has been obtained a nonpadded narrow anterior and posterior moulded plaster splint reinforced with circular

plaster is applied from the shoulder to the distal crease in the palm for radial traction and to the proximal interphalangeal joints for metacarpal traction. Pyramids of plaster incorporate the protruding pin.

Before attempting to correct the overriding of the rotated major fragments, the simultaneous rotatory approximation of the major fragments must be coordinated with firm traction. Where spiral or oblique fractures are rotated so that their cortical surfaces are in apposition the reposition of the fractured surfaces must be effected before attempting traction.

While it is obviously desirable to obtain a perfect realignment of the fragments, a 50 to 75 per cent approximation of the fracture surfaces is

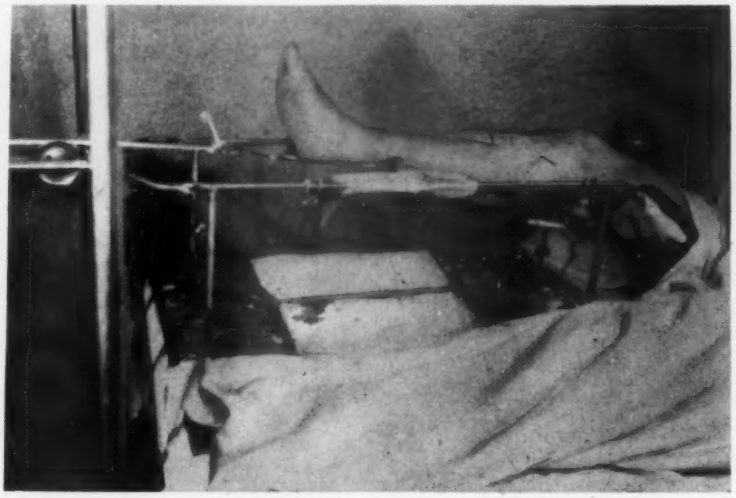


FIG. 6.—Boehler frame—through-and-through pin through tibia, two fingers' breadth above tip of internal malleolus; half pins inserted in sites of election. Ready for connecting rods, and application of moulded anteroposterior and circular encasement.

adequate if the rotation has been corrected and the proper long axis has been restored.

Compound Fractures.—With the limb fixed in traction the débridement and the reduction is facilitated. Whenever it is possible the original traction should be maintained until the patient is placed on the operating table. If feasible before cleansing, no attempt should be made to correct the rotation of the fragments or to exert so much traction that a protruding fragment is drawn back into the wound. While maintaining traction, the site selected for the insertion of a traction pin is scrubbed with green soap, washed with ether and alcohol and painted with tincture of iodine and alcohol. The traction pin is inserted, a dressing and the caliper is applied. The traction cord is fixed to the traction bar or placed over the pulley on the splint with barely enough traction to hold the fragments in position.

Sterile gauze is again placed over the wound, the extremity is cleansed as outlined above. The wound is débrided and the desired number of pins are inserted into the major fragments. The pins are locked to their con-

necting rods. The fragments are visually realigned into position by manipulating each fracture unit and exerting traction. The connecting rod is applied and locked to both fracture units. Where a self-realigning splint is available this procedure is greatly facilitated. Sulfanilamide crystals are sprinkled into the wound and vaselined gauze is laid lightly across the wound. A nonpadded encasement is then applied so as to adequately incorporate the adjacent joints. The connecting rods may be left on the pins or small pyramids of plaster are applied to incorporate the projecting pins. Subsequent changing of the plaster when necessary is facilitated by replacing the connecting rods. This assures against redisplacement while applying a new encasement.

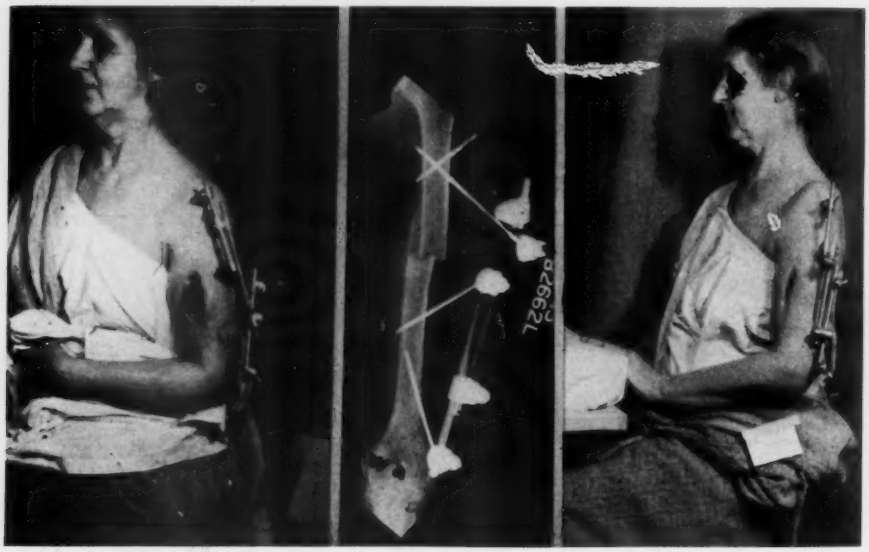


FIG. 7a FIG. 7b FIG. 7c

FIG. 7.—a. Débrided compound fracture of the humerus and external half pin fixation, February 15, 1943.
b. April 2, 1943—note extent of new bone formation.
c. April 2, 1943—before removal of pins. No infection of pin sites.

The principles of Orr and Trueta having been so well established in the Spanish Civil War, in the present world conflict, and in civil surgery, that we believe it *obligatory to apply plaster to completely immobilize the extremity,* thus assuring the physiologic rest and lymphatic stasis necessary in the proper treatment of compound and infected wounds. While we did successfully treat a compound fracture of the humerus without plaster, we do not believe repetition justified (Fig. 7—a, b and c). The occasional successful case of compound fracture treated by external pin fixation without plaster will only serve to encourage others to use a procedure which is sure to prove disastrous and only serve to discredit it.

III — COMPLICATIONS

(1) *Infection—Prevention.*—A discharge from the pin sites occurred in 37 cases (46 per cent). In many cases it was slight and was soon covered

with a crust, without actual suppuration. In some instances pus emanated from the bone and discharged for many months. In some cases the discharge persisted much longer than it required for the fracture site to heal (Figs. 8, 9 and 14d). We believe that the infection of the pin sites is the most serious potential and real complication when using external pin transfixion of fractures. *The infection far transcends the dangers of distraction, delayed union and nonunion.* The latter does not endanger the lives

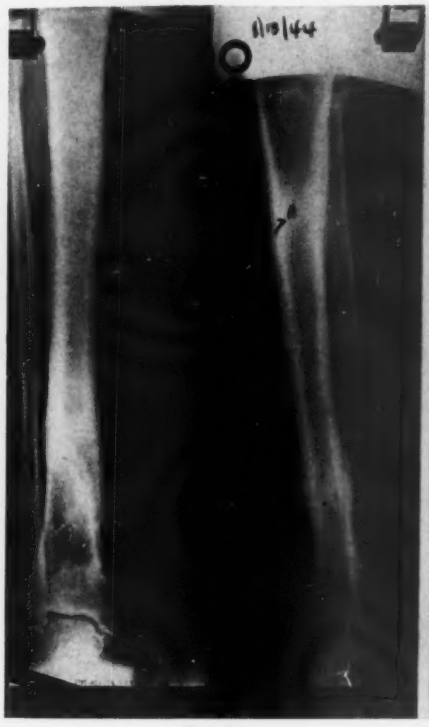


FIG. 8

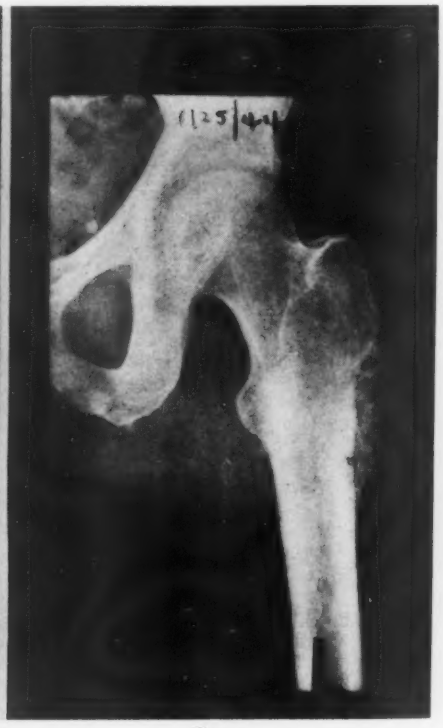


FIG. 9

FIG. 8.—Note sequestrum in pin site, discharge persisted for more than a year.
FIG. 9.—Fracture middle and lower third healed. Periostitis and large sequestrum subsequently removed from pin site.

of the patients and is more readily preventable or at least amenable to treatment with less hazard to the patient.

Most of our protracted infections and those that were fatal followed in those patients in whom the initial treatment did not include plaster.

To obviate external contamination of the pin sites as a source of infection we have been meticulous in our technic and have taken the precaution to seal over the pin sites. Nevertheless, we have seen what appeared to be an innocent nonsuppurative inflammatory exudate become purulent, extend along muscle and fascial planes, or into bone; and result in osteomyelitis. Or the infection may extend into the blood stream and may become fatal.

Even the use of plaster does not mitigate against infection of the pin sites. When the swelling subsides the plaster may be wholly ineffective in mobilizing the soft tissues.

Case Report.—In the case of J. D., who, on November 8, 1942, sustained a compound comminuted fracture of the tibia and the fibula, the wound had been débrided and the fragments transfixed with external pins and plaster. After having had a normal temperature for five days, it gradually reached 104° F. on the 9th day. Chemotherapy was ineffective and it was subsequently discontinued to eliminate drug fever. Examination of the compound wound revealed no evidence of infection. However, the encasement was very loose around the pins and there was extensive suppuration about the pin sites which required multiple incisions. Culture of the pin sites revealed mixed pyogenic organisms and *Cl. welchii*. Clinically, there was no evidence of gas gangrene. An encasement was reapplied. The patient's condition improved. In January, 1943, there was evidence of a metastatic involvement of the left acromioclavicular joint. Aspiration biopsy showed staphylococcus. Aspiration and immobilization in plaster was effective in controlling the pain and infective process. The pins were removed in two months, the pin sites healed in three months. Union was firm in seven months.

While the advantage of *ambulation* and early motion of joints would seem desirable, the inherent danger of infection of the soft tissue and bone from ambulation and unsupported soft tissue with plaster, is far too serious to recommend it as a routine procedure. *We believe that too much emphasis is laid on ambulation and joint motion.* The motion that accompanied the treatment of fractures of the femur with external fixation without plaster was not sufficient to justify subjecting these patients to the potential danger from infection. Only with the greatest difficulty could they be induced to get out of bed and use crutches. The friction of the pins against the soft tissues caused pain and a discharge at the pin sites in nine femoral fractures treated without plaster. Nor have we found that the ultimate restriction of the hip or knee after the use of plaster is any greater after the use of plaster than with the nonencasement treatment.

Certainly, in fractures of the tibia and fibula the desire of early motion of the knee or ankle is not a justifiable indication for the use of external pin fixation without plaster. In nine of the 54 fractures of the tibia and fibula we made a determined effort to use external pin fixation without plaster. After a few days the rigidity of the fragment could not be maintained. A discharge appeared at a pin site. While not always suppurative, its significance soon became apparent. Subsequent fixation of the extremity in plaster, from toes to the groin was necessary to limit the infection and to more rigidly fix the fragments and the pins. The mobility of the joints, while temporarily restricted in plaster invariably returned.

(2) *Distraction—Delayed Union—Prevention.*—We attribute the mobility of the fracture site in cases which we treated without plaster to (1) ambulation and joint motion; (2) to failure to properly transfix the fragments; (3) the elasticity of the pins (4) to the *pressure necrosis of the pins against the bone;* and (5) inadequate support of the soft tissues and pins with a short encasement. A pin became loose or the bone softened around the pin, and this impaired the stability of the fixation. As a result of the mobility of the fragments, decalcification of the fracture surfaces continued and a gap soon became apparent.

Fractures of the Tibia and Fibula.—In our efforts to more rigidly trans-

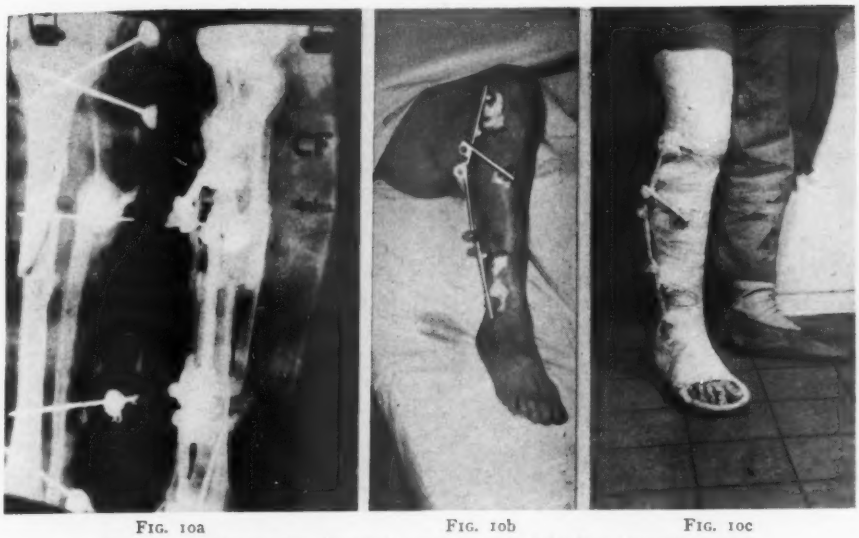


FIG. 10a FIG. 10b FIG. 10c

FIG. 10.—a. Intermediate fragment transfixed and joined to connecting rods.
b. External pin fixation—some mobility of fragments.
c. Immobilization in plaster incorporating transfixion pins.

FIG. 11a FIG. 11b

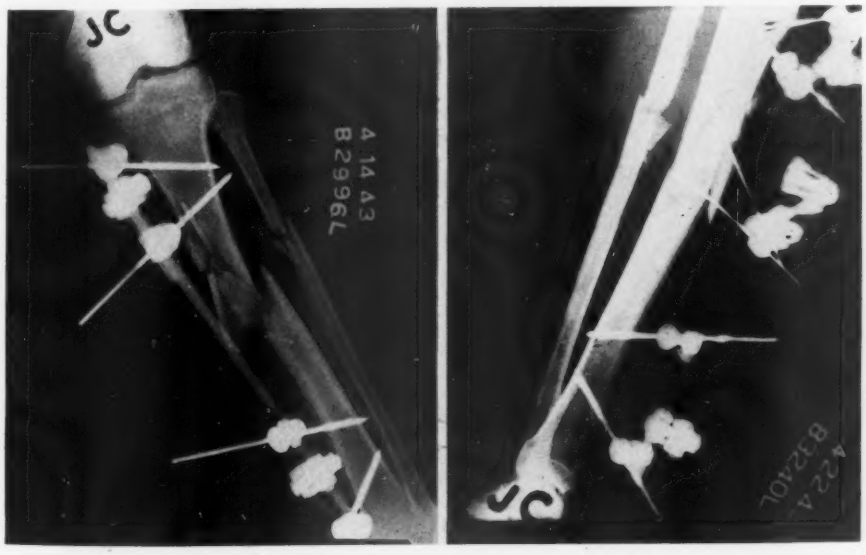
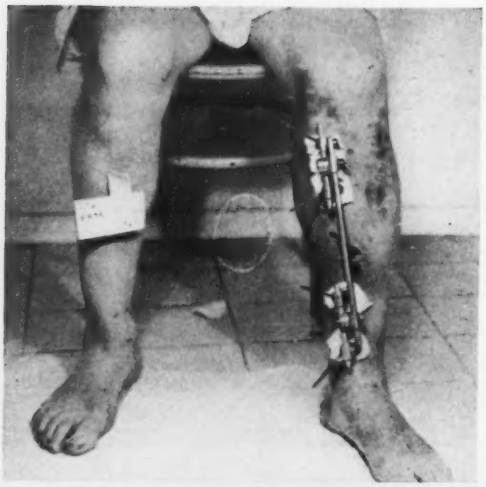


FIG. 11.—Comminuted fracture tibia and fibula, April, 1943.
a. Intermediate fragment slipped after transfixion of major fragments with Roger Anderson pins.
b. Roentgenogram—transfixion of intermediate fragment.

FIG. 11c



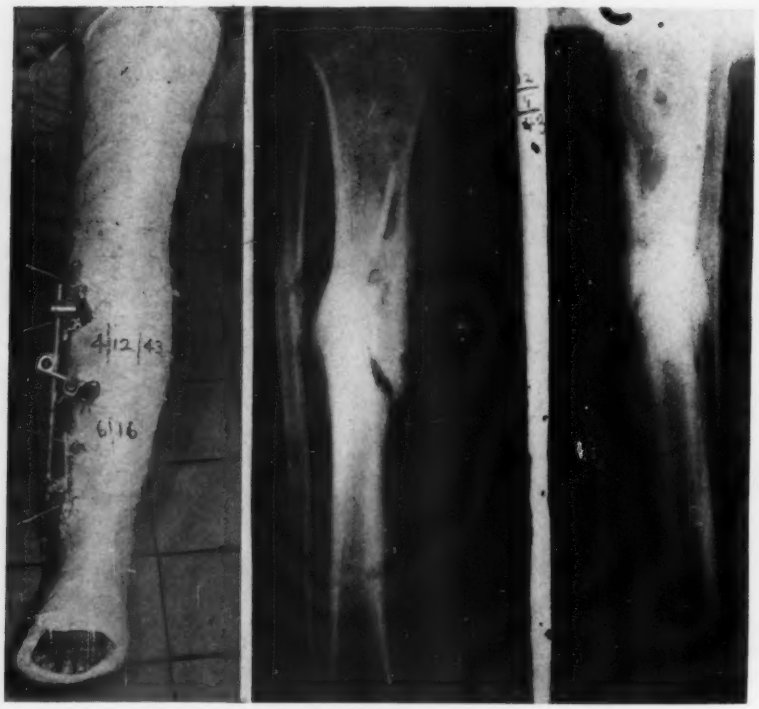
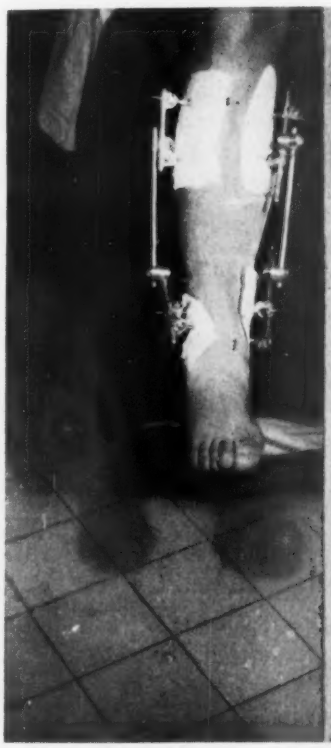


FIG. 11d FIG. 11e

FIG. 11.—c. Photograph of transfixion without plaster.
d. Mobility of fragments necessitated the use of plaster.
e. Roentgenogram December 9, 1943—evidence of union.

fix the major fragments without plaster we have employed a *transfixion pin across the fracture site* (Fig. 10—a, b and c). In comminuted fractures an effort was made to *transfix the intermediate fragment* to one of the major fragments (Fig. 11—a, b, c, d and e). We have also tried using four long through-and-through pins, the most proximal and distal pin being inserted at right angles to the longitudinal and transverse diameter of the tibia, while the others were inserted obliquely to the long and transverse axis of the



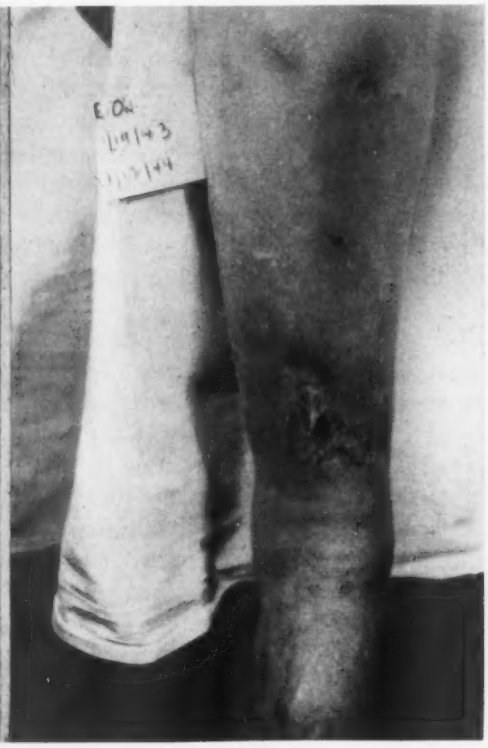


FIG. 12 FIG. 13

FIG. 12.—Four long through-and-through pins; the most proximal and distal pins are inserted at right angles to the longitudinal and transverse diameter of the tibia and the intermediate pins are inserted obliquely. Pins fixed with two sets of rods. Small plaster dressings applied around the pin sites.

FIG. 13.—Showing excoriation around the pin sites one year after the pins were inserted.

tibia (Fig. 12). With none of these procedures was either sustained impaction or immobility of the fracture sites obtained without plaster. The presence of long through-and-through pins, did not entirely eliminate the pressure necrosis and the softening of the bone around the pins or the infection at the site of the pin insertions (Fig. 13).

Application of Plaster.—In every instance of nonencased fixation of the fractures of the *tibia and fibula,* we had no alternative but to implement the fixation with plaster of paris, from the groin to the toes, and incorporate the pins in pyramids of plaster. This more effectively maintained immobility of the fragments, with a minimal exudate and infection of the pin sites.

Early Removal of the Pins.—The practice of keeping pins in the fragments until there is roentgenographic or clinical evidence of union is a contributing factor to infection, maintenance of the fragments in distraction and causing delayed union. Early removal of the pins is definitely indicated, to prevent sustained distraction, prevent infection of the pin sites, and to permit the involuntary muscular contraction to approximate the decalcifying fracture surfaces, even at the expense of some alteration in the position of the fragments in a new skin snug-fitting encasement. Loosening the bars, or cutting a circular section out of the encasement or adjusting the turn buckle has not resulted in satisfactory impaction, in our hands. Wedging of the encasement is of inestimable value in correcting the bowing or angulation.

Union of the tibia cannot keep pace with union of the vascularized muscular fractured fibula. While the pins may not keep the fibula fragments from uniting, they do prevent the muscles from impacting the poorly vascularized comminuted tibial fragments or the partially decalcified transverse fractures, during the period of active hyperemia. If the pins are removed after the fibula has united and the tibial fragments are not in contact, union of the tibia will be delayed.

To obviate the possibility of delayed union due to distraction of the fragments by the pins and to prevent further friction of the pins in the loose encasement, the pins should be removed at the end of the 3rd or 4th week in transverse fractures and in the 5th or 6th week in spiral, oblique or comminuted fractures. The connecting rods are reapplied, the anterior two thirds of the shell removed and a snug fitting encasement from the groin to the toes is applied, with the knee in 30° flexion. After the encasement has hardened, the connecting rods are removed and roentgenograms are made. If the position of the fragments remained unchanged, the pins are extracted. Where there is a loss of bony structure in compound fractures—the pins should be maintained in position to maintain length until the wound is healed and the wound is ready for bone graft.

Fractures of the Femur.—The problem of distraction and delayed union in fractures of the femur is not comparable to fractures of the tibia because of the ample blood supply to the femoral fragments. Distraction is a less serious concern in the oblique and spiral fractures because contact of the large fracture surfaces can be readily maintained. It is in this type of fracture that we had our most satisfactory results with the treatment without encasement.

It is in the cases of transverse and comminuted fractures that distraction with pins must be guarded against. The slightest movement resulting from the lack of immobility and sustained contact results in further decalcification of the fracture surfaces because of the continued hyperemia. A gap, which may be barely visible roentgenographically, may follow. This is in striking contrast to the large ossifying bony muscular hematoma which follows during the period of suspension with Russell traction. In Russell traction, the unopposed contracting muscles, which are one step ahead of any decalcification

which may result from shearing of the fragments, serves to impact the fractured surfaces.

IV — INCIDENCE OF INFECTION OF PIN SITES — AND THE TIME REQUIRED FOR THE PIN SITES TO HEAL

The incidence of discharges from the pin sites is summarized in Table I. Thirty-seven of the 80 cases, or 46 per cent, developed some discharge, which varied from a slight serous exudate to a frank purulent discharge.

In 19 of the 37 cases, the discharge gradually diminished and the pin sites healed within one to eight weeks after the extraction of the pins. In 18, or 22.5 per cent, there was a low grade infection of the bone, from which, in some instances, a sequestrum was extracted.

Fractures of the Humerus.—The pin sites, in three of the four simple fractures treated with external pin fixation, with a short plaster encasement, healed within two weeks after the extraction of the pins. There remained considerable edema and restriction of motion about the elbow for some time after the extraction of the pins in two cases.

In the compound fracture treated with external pin fixation, without plaster, there was no discharge or edema. The mobility of the shoulder and elbow was satisfactory during the period of transfixion and increased rapidly with the extraction of the pins.

Of the five fractures of the humerus treated by external pin fixation, the patient with the compound fracture, had the most satisfactory result as to freedom from pain, exudate and edema. The reason for the good result was: first, the proper insertion of the pins at the sites of election; second, the firm transfixion of the pins through the fragments; and third, compound fractures of the upper extremity are more amenable to treatment than lower extremity injuries. Nevertheless, we do not advocate the nonencased treatment for compound fractures of the humerus.

Fractures of the Tibia and Fibula.—Of the 54 simple and compound fractures, 16, or 29 per cent, developed an infection around the pin sites. In 12, or 22 per cent, an incision for drainage was necessary. Fourteen, or 26 per cent, developed an infection of the bone at the pin site.

Of the 31 simple fractures there was a discharge from the pin sites in ten, or 32 per cent. Incision and drainage was required in seven. The discharge persisted for three months in two; four months in two; five months in two; and four are discharging at the end of 13, 18, 18, and 21 months, respectively. Concentric sequestra was demonstrable in four, and roentgenographic evidence of an infectious process was ultimately evident in ten (Table II).

Of the 23 compound fractures, the pin sites discharged in six cases, or 26 per cent, and involved the bone in four. Incision and drainage was necessary in five. One patient, age 61, died in two and one-half months from cerebral thrombosis, pneumonia and cirrhosis of the liver and sepsis. The discharge persisted in one for three months; in two for four months; and in two for six months (Table III).

Fractures of the Hip.—All seven of the fractures of the neck and inter-

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TABLE II

SIMPLE FRACTURE TIBIA AND FIBULA

INCIDENCE OF INFECTION OF PIN SITES

COMPARATIVE TIME FOR PIN SITES AND FRACTURE SITE TO HEAL

Case No.		Age	Adm.	Pins 2	3	4	5	Pin Site Infected	Time for Pin Site to Heal	Infection in Bone	Time for Fracture to Heal	Followed	No Encasement	Encasement
1	H.B.	46	5/41			+					4 mos.	7 mos.		+
2	E.B.	69	12/42			+		+ I & D.*	Disch. 18 mos.	Yes (S)†	4 mos.	18 mos.	+	+
3	I.C.	61	8/42			+					5 mos.	18 mos.		+
4	H.C.	37	5/41			+					4 mos.	20 mos.		+
5	C.F.	47	8/42				+	+ I & D.	Disch. 5 mos.	Yes	7 mos'	18 mos.	+	+
6	S.F.	55	9/42		+						6 mos.	15 mos.		+
7	S.G.	44	1/41	+							3 mos.	13 mos.		+
8	T.H.	60	5/41	+							4 mos.	7 mos.		+
9	S.H.	14	10/42		+						3 mos.	6 mos.		+
10	J.H.	42	3/42			+					9 mos.	15 mos.		+
11	M.K.	65	12/42		+						3 mos.	10 mos.		+
12	J.K.	41	5/41		+			+ I & D.	Disch. 4 mos.	Yes	5 mos.	15 mos.		+
13	J.K.	61	3/43			+		+ I & D.	Disch. 3 mos.	Yes	4 mos.	13 mos.	+	+
14	E.K.	42	3/42			+					5 mos.	8 mos.		+
15	E.O.	46	1/43			+		+ I & D.	Disch. 15 mos.	Yes (S)	4 mos.	15 mos.	+	+
16	H.P.	63	11/42				+	+ I & D.	Disch. 4 mos.	Yes	5 mos.	16 mos		+
17	M.O.	41	9/41			+		+ I & D.	Disch. 5 mos.	Yes	3 mos.	15 mos.		+
18	J.S.	53	9/42			+		+	Disch. 21 mos.	Yes (S)	14 mos.	21 mos.		+
19	A.S.	35	10/42			+					3 mos.	16 mos.		+
20	A.S.	35	10/42			+		+	Disch. 18 mos.	Yes (S)	3 mos.	20 mos.		+
21	J.S.	63	4/42		+						9 mos.	12 mos.		+
22	P.P.	53	1/43	+							3 mos.	4 mos.		+
23	J.C.	45	4/43				+				5 mos.	8 mos.	+	+
24	W.L.	45	4/43			+					4 mos.	5 mos.		+
25	F.A.	69	4/43				+				4 mos.	10 mos.		+
26	W.F.	50	9/43			+					4 mos.	8 mos.		+
27	J.L.	63	8/43		+						4 mos.	12 mos.		+
28	H.N.	42	8/43			+		+	Disch. 3 mos.	Yes	4 mos.	12 mos.		+
29	A.O.	47	9/43			+					4 mos.	9 mos.		+
30	M.C.	38	12/43			+					4 mos.	6 mos.		+
31	H.H.	56	12/43			+					6 mos.	6 mos.		+
Summary				3	6	18	4	10 7	4 disch. 15-21 mos. 2 disch. 3 mos. 2 disch. 4 mos. 2 disch. 5 mos.	10 4 (S)	7- 3 mos. 13-4 mos. 5- 5 mos. 1- 6 mos. 1- 7 mos. 2- 9 mos. 1-14 mos.		5	31

* I & D—Incision and drainage. † S—Sequestrum.

TABLE III

COMPOUND FRACTURE OF TIBIA AND FIBULA

INCIDENCE OF INFECTION OF PIN SITES

COMPARATIVE TIME FOR PIN SITES AND FRACTURE SITES TO HEAL

Case No.		Age	Adm.	Pins 2	3	4	5	Pin Site Infected	Sequestrum Pin Site	Time For Pin Site to Heal	Without Encase.	With Encase.	Time for Fracture to Heal	Followed	Osteomyelitis Fracture Site
1	J.B.	52	11/42		+			+ I & D.*	+	6 mos.		+	7 mos.	12 mos.	+
2	A.C.	61	5/41			+		+ I & D.		Died		+	Died—2.5 mos.		
3	J.C.	30	7/41			+					2 mos.	+	4 mos.	8 mos.	
4	J.D.	57	11/42				+	+ I & D.		3 mos.		+	7 mos.	13 mos.	+
5	W.H.	53	2/43			+		+	+	6 mos.	2 mos.	+	6 mos.	12 mos.	+
6	E.L.	58	12/41			+					1 mo.	+	8 mos.	2 yrs.	+
7	H.L.	57	9/42		+							+	7 mos.	11 mos.	
8	J.R.	57	6/42			+						+	19 mos.	24 mos.	
9	J.S.	30	12/42			+						+	3 mos.	18 mos.	
10	L.S.	45	11/42		+							+	4 mos.	12 mos.	
11	J.S.	50	7/41			+					2 mos.	+	15 mos.	20 mos.	
12	W.S.	33	10/42	+								+	4 mos.	14 mos.	
13	J.V.	49	5/42		+							+	Ununited	2 yrs.	
14	M.W.	39	1/42			+						+	2 yrs. Bone graft	29 mos.	+
15	E.W.	48	1/41	+								+	1 yr.	20 mos.	+
16	J.Z.	50	1/41	+				+ I & D.	+	4 mos.		+	3 yrs. Ununited graft	3.5 yrs.	+
17	M.F.	60	3/43			+						+	3 mos.	10 mos.	
18	R.L.	43	1/43		+							+	11 mos.	15 mos.	
19	J.O.	54	3/43			+						+	9 mos.	10 mos.	
20	S.R.	20	1/43			+		+ I & D.	+	4 mos.		+	7 mos.	10 mos.	
21	F.S.	68	6/43			+						+	7 mos.	9 mos.	
22	B.S.	54	9/43			+						+	5 mos.	6 mos.	
23	M.B.	45	12/43			+						+	Under treat.	6 mos.	+ (old)
	Total			3	5	14	1	6 5	4	1–3 mos. 2–4 mos. 2–6 mos.	4	23	3– 6 mos.—7 7–12 mos.—9 15–19 mos.—2 Ununited 3		8

* I & D.—Incision and drainage.

* I & D—Incision and drainage. † S—Sequestrum.

1- 6 mos.
1- 7 mos.
2- 9 mos.
1-14 mos.

trochanteric region treated by external pin fixation without plaster developed some discharge at the site of the pin insertion. Every effort was made to keep the pin sites meticulously clean. Five patients subsequently developed general sepsis and died. The discharge from the other two ceased in a few days after extracting the pins.

External pin fixation without plaster for fractures about the hip is a hazardous procedure. If a plaster spica is applied to implement external pin fixation in elderly people, we would be reverting back to chaining the patient to the mattress, with its potential complications. In a report, on "Fractures of the Neck of the Femur: An Analysis of 157 Cases," we stated that other than expediting the procedure of immediate transfixion and minimizing the trauma in the process of fixation, external pin fixation had no advantage over internal fixation. The incidence of infection and sepsis was too high; the nursing care was increased; and the patients were apprehensive and refused to be ambulatory because of the pain in the region of the pin sites. There was a constant dread of infection. The patient could not be discharged from the hospital with the protruding apparatus. The uniformly good results with internal fixation of fractures about the hip, does not justify subjecting patients to the hazards of external pin fixation.

Fractures of the Shaft of the Femur.—Nine of the 12 simple fractures, or 75 per cent, developed a discharge from one or more of the pin sites (Table IV). In five the pin sites healed within a few days, or weeks, after extraction of the pins. One discharged for one month; one for seven months; one for eight months; and another for 13 months. In three there was a destructive bony process at the pin sites, in two of whom a sequestrum was removed.

In three instances, the pins were extracted before union was complete because of an infection of the pin sites. The extremities then were suspended in Russell traction. No redisplacement of the fragments resulted. In one, the infection subsided with the removal of the pins. In another it required seven months after sequestrectomy and immobilization in a plaster spica, and penicillin, to control the infection. In the third (M. H., age 76) there was a low grade destructive process in the bone at the distal pin site. Eight months after the original fracture she sustained a fracture through the discharging distal pin site below the healed original fracture site. She died several days later from pulmonary embolism.

V — RELATION OF THE HEALING TIME OF THE FRACTURE SITE TO THE TIME REQUIRED FOR THE PIN SITES TO HEAL

As shown in Tables II, III, and IV, the pin sites continued to drain in many cases as long as it took the fracture to heal. In some instances the pin sites drained long after the fracture was united.

There were five simple fractures of the tibia and fibula which continued to drain with a variable amount of edema and excoriation after the fracture site healed. Two fractures which were healed in three months continued to drain, one for five months and the other for 16 months; another was healed

TABLE IV

FRACTURES OF THE FEMUR

INCIDENCE OF INFECTION OF PIN SITES

COMPARATIVE TIME FOR PIN SITES AND FRACTURE SITES TO HEAL

Case No.	Age	Adm.	Pins 3	Pins 4	Pins 5	Pin Fixation No Encase.	Pin Fixation Encase.	Subsequent Treatment Russell Traction	Subsequent Treatment Encase.	Operation and Pin Fixation	Discharge from Pin Site	Time for Pin Site to Heal	Time for Fracture to Heal	Followed
1 M.H.	76	5/43		+		4 mos. short		2 mos.			Osteomyelitis —fracture through pin site—8 mos.	Discharged until death at 8 mos.	6 mos.	Died. Pulmonary embolism
2 R.L.	52	11/43		+		18 days		3 mos.	4 mos.		Osteomyelitis	7 mos.	4 mos.	7 mos.
3 S.C.	59	2/43		+		5 wks.			3 mos.	Encase. 11 mos. Osteomyelitis	13 mos. Osteomyelitis	13 mos. (I & D.)	9 mos. (Osteomyelitis)	14 mos.
4 R.D.	35	1/43			+	4 mos.			Encase. 5 mos. —then	9th month. Dual onlay graft—Haynes pins—no encase.—5 mos. union	Yes (I & D.)	Few days	14 mos. (Osteomyelitis) —graft	15 mos.
5 T.D.	48	12/42			+	3 mos.					Yes	Few days	4 mos.	6 mos.
6 J.G.	57	8/42	+				Spica 4 mos.				Yes	Few days	4 mos.	15 mos.
7 M.J.	28	12/42		+		3 mos.					Yes	2 wks.	4 mos.	4 mos.
8 P.P.	49	8/42			+	3 mos.					No		4 mos.	15 mos.
9 E.R.	55	3/43			+	3 mos.				No encase.	Yes I & D.	Few days	4 mos.	9 mos.
10 A.T.	105	10/42		+		2 days								Died— 2 days
11 K.Mc.	54	5/42			+		Spica 4 mos.				No		4 mos.	14 mos.
12 J.Mc.	58	9/43		+		2 mos. short		2 mos.			Yes	1 mo.	4 mos.	6 mos.
13 J.H.	56	10/43			+		Spica 5 wks.			Débridement	Yes			Died. Multiple injuries
Total			1	6	6	10	3				10			

in 14 months, and drained 17 months. Two fractures were healed in four months and drained, one for 13 and the other for 15 months. Five others continued to drain about as long as it required for the fracture to heal; in two cases the pin sites drained for three months, and the fracture was healed in four months; in two others the pin sites drained for four months, and the fracture was healed in five months; while one pin site drained for seven months, and the fracture site healed in seven months.

In the compound tibial fractures, the pin sites healed before the fracture sites. In one, the pin site drained for three months, two drained for four months, and two for six months. Many of these fractures were extensively comminuted; there was less manipulation, less trauma at the pin sites and in most instances they were immediately immobilized in plaster, to which, we attribute the earlier healing of the pin sites.

The pin sites in three of the cases of fractured femur continued to discharge long after the fractures were healed. One was discharging at the end of eight months, two months after the fracture had healed, when the patient sustained a new fracture which extended through the discharging distal pin site below the original healed fracture site. In another patient, the discharge from a pin site persisted for seven months, which was three months after there was roentgenographic and clinical evidence of union of the fracture site. The third case, a badly comminuted fracture was united at the end of nine months but continued to drain for another four months from the proximal pin site from where a sequestrum had been partially removed.

VI — TIME REQUIRED FOR HEALING OF FRACTURES TREATED BY EXTERNAL PIN FIXATION

In evaluating the time required for the healing of fractures treated by external pin fixation it would be desirable to compare the time required to heal a similar group of cases treated by other procedures. Watson Jones and Coltart have recently reported the results of their treatment of fractures by various procedures. From our experience we are fully in accord with these observers that external pin fixation is a contributing factor in delaying union by maintaining the fragments in distraction.

It is obviously difficult to evaluate reports of the treatment of fractures. Most of the fractures we are reporting were badly comminuted and in individuals past 45 years of age. There is one very pertinent factor which we have observed in reviewing our cases, namely, that the less additional trauma we inflict on the fractured limb the sooner will the fracture unite. Our best results with femoral shaft fractures have followed with Russell traction. While in fractures of the tibia and fibula, the Kirschner wire in the os calcis, Boehler frame and plaster has given us our most satisfactory results.

Union followed in the majority of femoral shaft fractures in three to four months; unsupported weight bearing had to be guarded for another four to eight weeks. Because of pain in the region of the pin sites, it was with great reluctance that some of the patients could be gotten out of bed to

become ambulatory and move their joints. When plaster was used with the pins the mobility of the joint was equally slow in returning. This is in striking contrast to those cases treated in Russell traction. Russell traction was generally discontinued in two to three months. Quadriceps exercises were instituted soon after the traction was applied. Ambulation with crutches was permitted soon after discontinuing traction and the range of mobility of the joints was generally satisfactory at the end of the fourth month when in many cases crutches could be dispensed with.

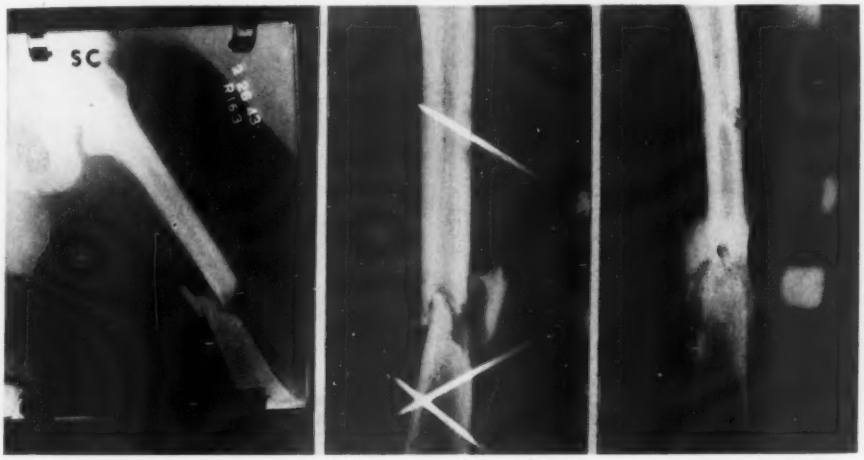

FIG. 14a FIG. 14b FIG. 14c

FIG. 14.—a. Roentgenogram on February 26, 1943—note comminution and rotation of intermediate fragment.
b. April 26, 1943—fixation with half pins—open operation, impaction of major fragments; note sequestrum in distal pin site of the proximal fragment.
c. March 3, 1944—another sequestrum still present at fracture and pin sites.

The high incidence of slow union in tibial fractures was most noticeable in the cases in which the pins were left in for two months, or longer. This has become less apparent with the early removal of the pins and continued immobilization from toes to groin plaster with the knee in 30° flexion. Of the simple fractures, seven healed in three months, 13 in four months, five in five months, one in six months, one in seven months, two in nine months and one in 14 months. In the compound fractures slow union was particularly noticeable; seven united in from three to six months, nine required seven to 12 months, two from 15 to 19 months and three were ununited fractures at the end of two years, two of which were grafted.

VII — INCIDENCE OF INFECTION OF THE FRACTURE SITE FOLLOWING OPEN OPERATION WITH EXTERNAL PIN FIXATION WITHOUT PLASTER

Femurs.—In three patients, because of the persistent displacement, the fracture site was exposed and the fragments were transfixed with fracture units without plaster.

In one patient (Case 3) an infection developed at the fracture and pin sites. Sequestra were incompletely removed and the discharge persisted

FIG. 15a

FIG. 15b

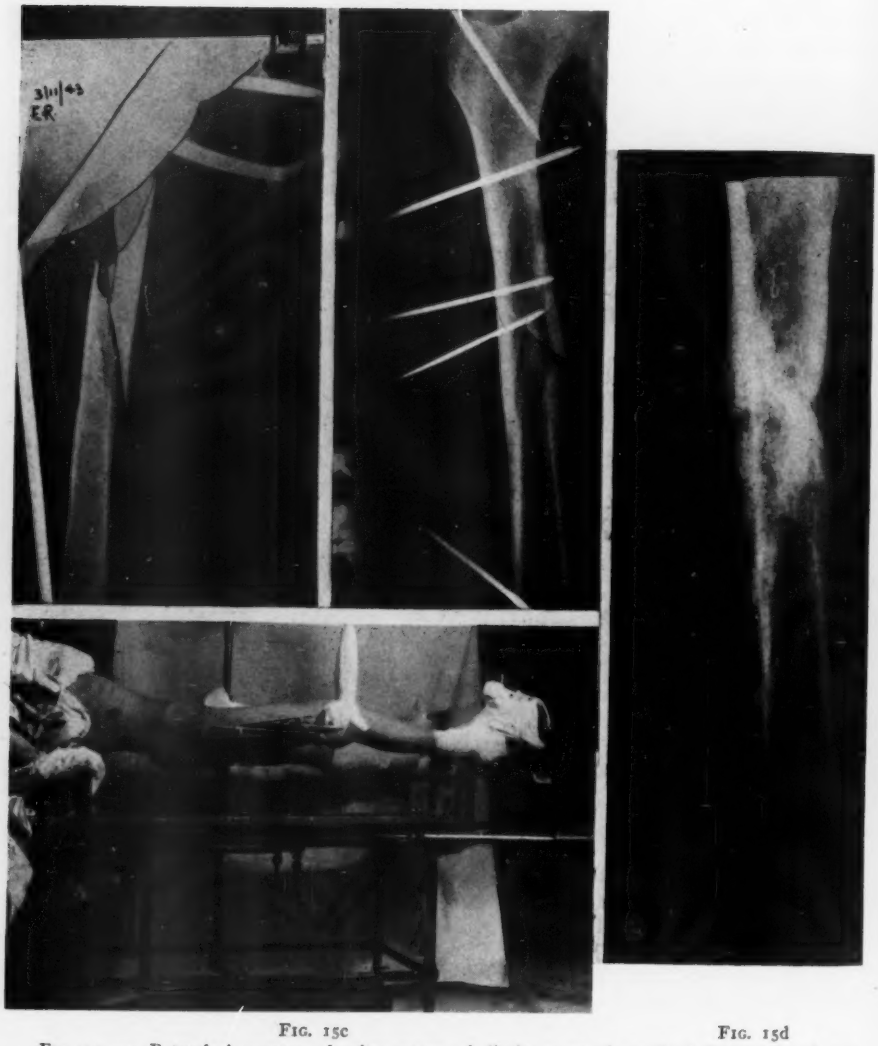

FIG. 15c

FIG. 15d

FIG. 15.—a. Retouched negative showing extent of displacement of proximal fragment and comminution on admission March 11, 1943.
b. April 6, 1943—after transfixion of major and intermediate fragments.
c. Reduction on Hawley table—note extra connecting rods.
d. December 10, 1943—extent of union nine months later.

from both sites for 13 months although the fracture site has been firm for four months (Fig. 14—a, b and c). In another patient (Case 9) an infection of the site of the incision healed within a few days after the pus was evacuated (Fig. 15—a, b, c and d). The third patient (Case 4) was admitted from another institution, three months after the injury, with an ununited comminuted fracture. This had previously been fixed with three Parham bands. The bands were removed and the fragments were transfixed with Roger Anderson fracture units. One month later two Steinman nails were inserted

into the fractured neck of the femur and connected to the proximal fracture unit. An infection developed in the region of the pins that were inserted into the hip. The infection healed in a few days after extracting the hip pins. Four months after transfixion of the shaft of the femur the pins were removed. There was no evidence of union of the major fragments. A plaster spica was applied. Five months later there was still no evidence of union. A dual onlay graft was fixed to the major fragments with vitallium screws and the fragments were transfixed with Haynes pins, without plaster. Five months

FIG. 16a FIG. 16b FIG. 16c

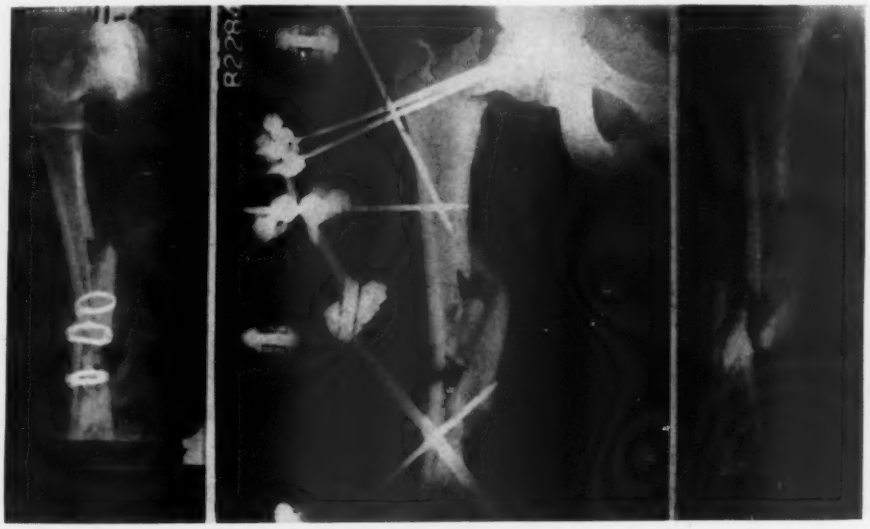

FIG. 16.—a. Injury October 27, 1942. Transferred to Bellevue Hospital January 23, 1943—with Parham bands and plaster.
b. Parham bands removed January 29, 1943—nonunion; distal major and intermediate fragments transfixed with aid of Roger Anderson anatomical splint.
c. October 2, 1943—distal fragment ununited.

later the Haynes pins were removed. There was evidence of union. There was no discharge from the pin sites during the five months. There was, however, a low grade infection of the wound. Two months later the vitallium screws and a small devitalized fragment of the graft were removed. The screw sites were clean. The wound was treated with penicillin locally and penicillin was given intramuscularly. Fourteen days later the wound was practically healed (Fig. 16—a, b, c, d, e and f).

Humerus.—External pin fixation units were used on an ununited fracture of the middle and lower third of the humerus in a man, 38 years of age. He sustained the fracture in January, 1943. He was plated in Africa the same day. In June he was admitted with a gap between the fragments. The Lane plate was removed; an onlay graft was fixed to the fragments with vitallium screws. The fragments were also transfixed with Roger Anderson pin units and the extremity was incorporated in plaster. The pins were removed in ten weeks because of some edema about the distal pin sites. This

FIG. 16d

FIG. 16e

FIG. 16f

FIG. 16.—d and e. Roentgenogram and photograph in January, 1944. Dual onlay grafts, vitallium screws. Haynes pins applied October 10, 1943. Slight discharge from wound. Pin sites clean.
f. Roentgenogram April, 1944. Pins removed March 21, 1944. Pin sites clean; clinical and radiographic evidence of union. Very slight discharge from operative incision. June 2, 1944, screws removed, sites clean. Small fragment of graft necrotic removed. Fracture healed. Penicillin locally and intramuscularly. June 12—slight discharge.

disappeared with the removal of the pins. Union was firm in four months. No infection developed. He has been followed one year (Fig. 17—a, b and c).

COMMENT.—After an open reduction for a fracture of a long bone and transfixion of the fragments with pins, a plaster encasement adequately immobilizing the extremity should be applied.

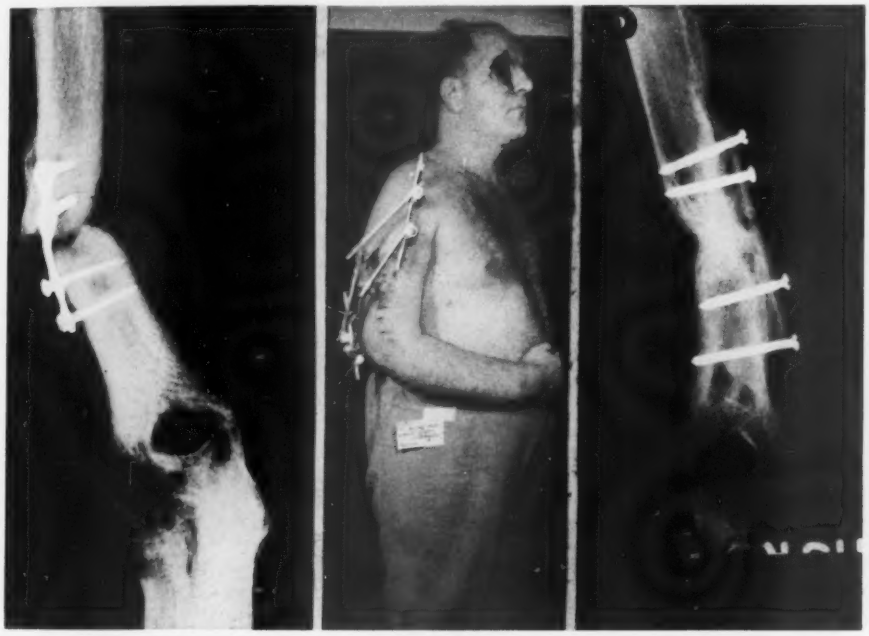

FIG. 17a FIG. 17b FIG. 17c

FIG. 17.—Case F. P., age 38. Fractured humerus plated, in Africa, June 22, 1943.
a. Roentgenogram June 10, 1943—nonunion—Lane plate holding fragments in distraction.
b. Photograph September 23, 1943 after removal of Lane plate and insertion of onlay graft Vitallium screws and external pin fixation with Roger Anderson fracture units.
c. December 20, 1943—six months later—extent of union.

When a bone is grafted and the graft is transfixed with vitallium screws, it is imperative that a plaster encasement be applied to adequately immobilize the extremity. External pins, for the purpose of increasing the stability of the fragments, introduces a potential hazard, which should be avoided.

VIII — INDICATIONS FOR THE USE OF EXTERNAL PIN FIXATION

External pin fixation with or without plaster is not indicated when a more conservative procedure can be used which will give a good clinical result without subjecting the patient to the potential complications of external pin fixation.

(1) *In selected problem compound fractures:* when, in the surgeon's opinion, immobilization in plaster or distal pin traction and plaster, will not maintain a satisfactory realignment of the fragments, then, the procedure may be used with plaster adequately immobilizing the extremity (Fig. 18—a, b, c and d).

(2) *In infected fractures with persistent displacement:* to realign the

FIG. 18a

FIG. 18b

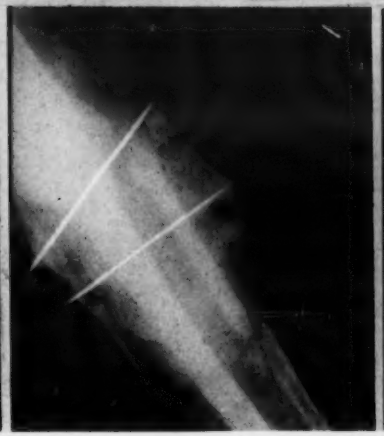

FIG. 18c

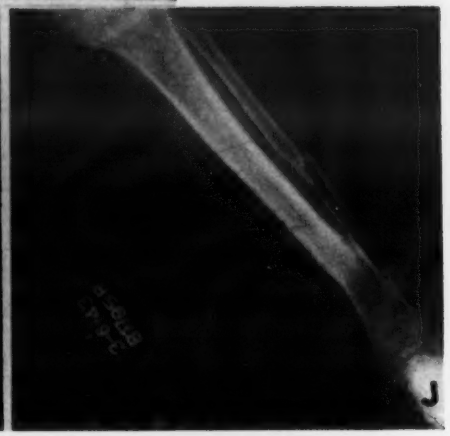

FIG. 18d

FIG. 18.—a. Patient age 50. Admitted, July, 1941, in shock, stupor, fractured ribs, dislocated left elbow, subluxation of right knee, Colles's fracture and a compound fracture of the lower third of the left tibia and fibula—treated for shock—transfixion pins without anesthesia, no débridement, sulfanilamide crystals.

b. Roentgenogram on admission.

c. Transfixion pins and plaster.

d. Roentgenogram March 6, 1943—firm union.

FIG. 19a

FIG. 19b

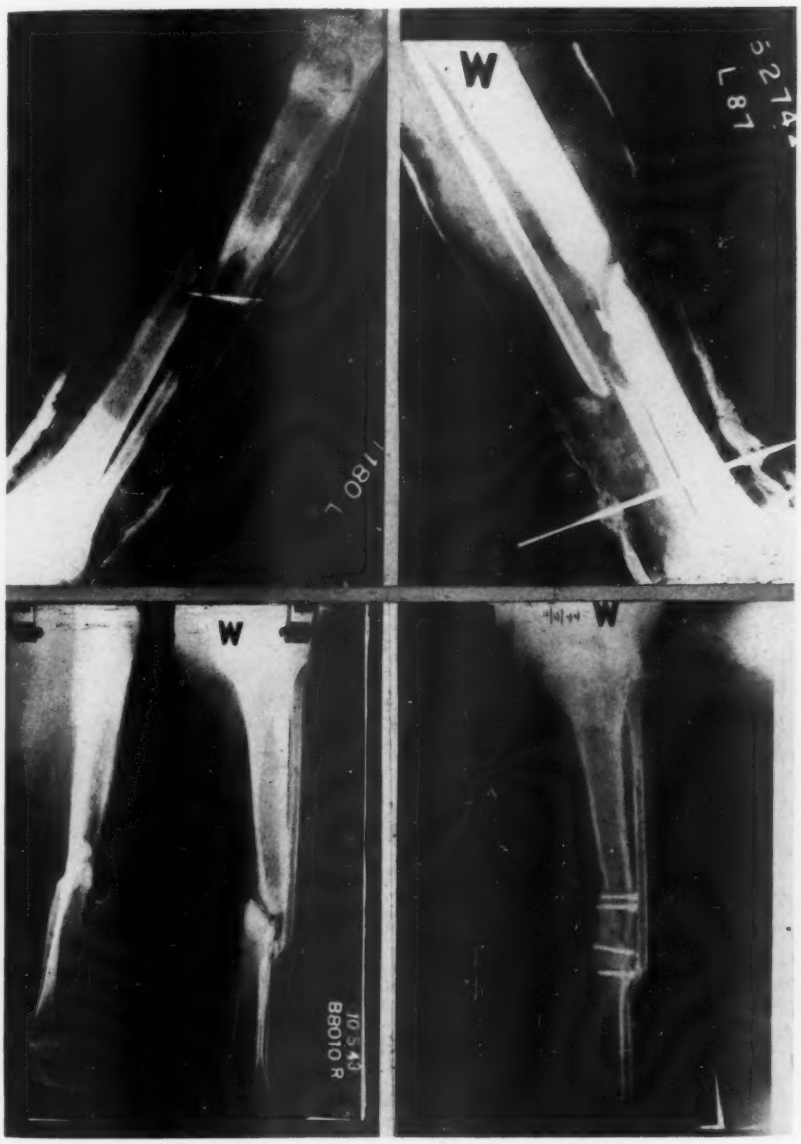

FIG. 19c

FIG. 19d

FIG. 19.—a. Patient age 39. Sustained a compound fracture of the middle third of the left tibia and fibula on January 1, 1942. Admitted to Bellevue Hospital January 31, 1942. Roentgenogram on February 1, 1942—one inch of overriding tibia protruding through infected wound.

b. Roentgenogram May 25, 1942 after realignment with Roger Anderson pins and anatomical splint—sequestrum of proximal end of distal tibial fragment.

c. Roentgenogram October 15, 1943—sclerosed ends of bone six months after wound was healed.

d. Roentgenogram showing dual onlay bone graft and vitallium screws. Encasement removed April 1944—firm union. Very slight discharge. Screws out May, 1944. June, 1944, wound healed.

fragments and to maintain them in position with the aid of plaster until there is sufficient union to permit the extraction of the pins (Fig. 19—a, b, c and d).

(3) *In compound and infected fractures,* in which there is a loss of bone external pin fixation and plaster can be used to maintain length until the wound has been healed sufficiently long to permit the insertion of a bone graft.

(4) (a) *Simple fractures:* Mechanical pin fixation with plaster may be used when conservative treatment fails to adequately correct rotation, restore

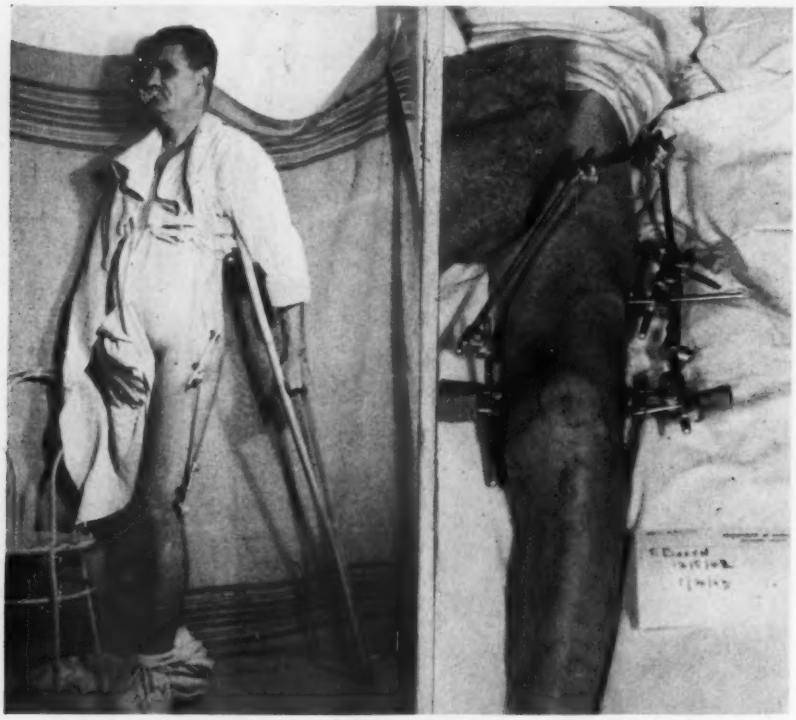

FIG. 20a FIG. 20b

FIG. 20.—a. Half pins for spiral and oblique fracture of the femur.
b. Half pins in the proximal fragment; two through-and-through pins in the low supracondylar fragment and a transfixion pin in the lower end of the proximal fragment.

the proper long axis of the fragments, approximate some of the fracture surfaces of a transverse fracture or approximate a displaced intermediate fragment.

(b) *Simple fractures of the shaft of the femur,* external pin fixation without plaster, or with a short encasement, permitting ambulation on crutches, may be employed only *with the patient fully aware of the potential hazards* and the surgeon is thoroughly familiar with the procedure (Fig. 20—a and b).

CONCLUSIONS

In 80 cases of external mechanical pin fixation of fractures the high incidence of discharge from the pin sites (46 per cent), of osteomyelitis of

the pin sites with persistence of discharge long after the fracture had united (22.5 per cent), and of deaths (10 per cent) should preclude the further use of the method as a routine procedure for fractures of the long bones and of the neck of the femur. The procedure should be used only in selected cases and by those who have been specially trained in the technic.

The potential dangers, of infection of the sites of the pin insertions, far transcends the dangers of distraction, delayed union and nonunion. The latter does not endanger the lives of the patients and is more readily preventable and amenable to treatment.

It should be restricted to certain problem fractures and to persistently displaced compound fractures, in which, by visual manipulation, the reduction can be facilitated and maintained, until a properly fitting encasement can be expected to maintain the realignment of the fragments.

Too much emphasis has been laid on ambulation and joint motion. Ambulation and early mobilization of joints should not be the motivating factors for the use of external mechanical pin fixation.

Infection of the pin sites and distraction and delayed union are attributed to (1) ambulation and motion of joints without plaster; (2) friction of the soft tissues against a pin which causes the infection and osteomyelitis; (3) *pressure necrosis* of the bone by a pin which impairs the stability of the fixation, permitting a continuous hyperemia of the fracture site with absorption of the ends of the bone, resulting in distraction of fragments; (4) the prolonged use of the pins; (5) failure to immobilize adequately the extremity and pins in plaster; and (6) failure to reapply a snugger encasement when the swelling subsides.

BIBLIOGRAPHY

Anderson, Roger: Fractures of the Radius and Ulna: A New Anatomical Method of Treatment. J. Bone & Jt. Surg., **16**, 379, 1934.

Idem: An Ambulatory Method of Treating Fractures of the Shaft of the Femur. Surg., Gyn. & Obst., **62**, 865, 1936.

Idem: An Automatic Method of Treatment for Fractures of the Tibia and Fibula. Surg., Gyn. & Obst., **58**, 639, 1934.

Idem: Ambulatory Method of Treating Femoral Shaft Fractures, Utilizing Fracture Table for Reduction. Am. J. Surg., **39**, 538, 1938.

Idem: Fractures of the Humerus. Surg., Gyn. & Obst., **64**, 919, 1937.

Anderson, R., and Burgess, E.: Delayed Union and Nonunion. Jour. Bone & Jt. Surg., **25**, 427, 1943.

Anderson, R., and Finlayson, B. L.: Sequelae of Transfixation of Bone. Surg., **13**, 46, 1943.

Anderson, R., McKibbin, W. B., and Burgess, E.: Intertrochanteric Fractures, Nonoperative, Castless, and Ambulatory Method of Treatment. Jour. Bone & Jt. Surg., **25**, 153, 1943.

Anderson, R., and O'Neil, G.: Comminuted Fractures of the Distal Ends of the Radius. Surg., Gyn. & Obst., **78**, 434, 1944.

Boyd, H. B.: The Treatment of Difficult and Unusual Nonunions. Jour. Bone & Jt. Surg., **25**, 535, 1943.

Bradford, C., and Wilson, P. D.: Mechanical Skeletal Fixation in War Surgery. Surg., Gyn. & Obst., **75**, 468, 1942.

Burns, B. H., and Young, R. H.: Time of Union in Fractured Tibia. Lancet, **243**, 299, 1942.

Davis, A. G.: Pin Distraction as the Cause of Nonunion. Jour. Bone & Jt. Surg., **25**, 631, 1943.

Griswold, R. A.: Fractures of Both Bones of the Leg: Treatment by a Modified Boehler Method with a New Apparatus. J. A. M. A., **104**, 35, 1935.

Griswold, R. A., and Holmes, G. W.: Double Pin Skeletal Fixation in Fractures of the Leg. Surg., Gyn. & Obst., **68**, 573, 1939.

Haynes, H. H.: Treating Fractures by Skeletal Fixation of the Individual Bone. Southern Med. J., **32**, 720, 1939.

Idem: Skeletal Fixation of Fractures. Am. J. Surg., **59**, 25, 1943.

Lewis, K. M., Breidenbach, L., and Stader, O.: The Stader Reduction Splint for Treating Fractures of the Shafts of the Long Bones. ANNALS OF SURGERY, **116**, 623, 1942.

Mazet, R.: The use and abuse of the anatomic splint in the treatment of fractures of the lower extremity. Jour. Bone & Jt. Surg., **25**, 839, 1942.

Miller, O. L.: Blind Nailing of the "T" Fracture of the Lower End of the Humerus which Involves the Joint. J. of Bone & Jt. Surg., **31**, 3, 1939.

Miller, O. L.: Simplified Internal Fixation of Inlay and Onlay Bone Grafts. J. Bone & Jt. Surg., **21**, 3, 1939.

McKibbin, W. B.: An Ambulatory Method of Treatment for Intertrochanteric Fractures of the Femur. Surg., Gyn. & Obst., **76**, 343, 1943.

Murray, C. R.: The Timing of the Fracture Healing Process. J. Bone & Jt. Surg., **33**, 2, 1941.

Orr, H. W.: Osteomyelitis and Compound Fractures. St. Louis; C. V. Mosby Co., 1929.

Idem: The Treatment of Compound Fractures. Arch. Surg., **40**, 825, 1940.

Idem: Compound Fractures. Am. Jour. of Surg., **46**, 733, 1939.

Idem: Determining Factors in the End-Results Following War Wounds and Compound Fractures. Bull. of the N. Y. Acad. of Med., 237, 1942.

Idem: Wounds and Fractures: Charles C. Thomas, 1941.

Reich, R. S.: Treatment of Intercondylar Fractures of the Elbow by Means of Traction. J. Bone & Jt. Surg., **18**, 997, 1936.

Shaar, C. M., and Kreuz, F. P.: Treatment of Fractures and Bone and Joint Surgery with the Stader Reduction Fixation Splint. Surg. Clin. North Am., **22**, 1537, 1942.

Siris, Irwin E., and Ryan, John D.: Fractures of the Neck of the Femur: An Analysis of 157 Cases. Surg., Gyn. & Obst., **78**, 631, June, 1944.

Trueta, J.: The Principles and Practices of War Surgery. St. Louis. C. V. Mosby Co. 1943.

Trueta, J., and Barnes, J. M.: Absorption of Bacteria and Toxins from the Tissues. Lancet, **1**, 623, 1941.

Idem: Immobilization in the Treatment of Infected Wounds. Brit. Med. Jour., **2**, 46, 1940.

Van Gorder, G. W.: Surgical Approach in Supracondylar Fractures of the Humerus Requiring Open Reduction. Jour. Bone & Jt. Surg., **22**, 278, 1940.

Watson-Jones, R., and Coltart, W. D.: Slow Union of Fractures: 804 Fractures of the Tibia and Fibula. Brit. Jour. Surg., **30**, 260, 1943.

Wilson, M. J., and Cantwell, A. R.: The Double Pin Method in the Treatment of Fractures of the Tibia and Fibula. Am. J. of Surg., **56**, 445, 1942.

BOOKS RECEIVED

TEXTBOOK OF GENERAL SURGERY. By Warren H. Cole, M.D., and Robert Elman, M.D. 4th edit. D. Appleton-Century Co., New York, 1944.

TEXTBOOK OF GYNECOLOGY. By J. H. Peel, M.A., B.M., B.Ch. (Axori), F.R.C.S., M.R.C.O.G. New York: Grune and Stratton, 1944.

INTRAVENOUS ANESTHESIA. By R. Charles Adams, M.D., C.M., M.S. (Anes.). New York: Paul B. Hoeber, Inc., 1944.

INDUSTRIAL OPHTHALMOLOGY. By Hedwig S. Kuhn, M.D. St. Louis: C. V. Mosby Co., 1944.

VASCULAR RESPONSES IN THE EXTREMITIES OF MAN IN HEALTH AND DISEASE. By David I. Abramson, M.D. Chicago: University of Chicago Press, 1944.

SMALL COMMUNITY HOSPITALS. By Henry J. Southmayd and Geddis Smith. New York: The Commonwealth Fund, 1944.

VIRUS DISEASES IN MAN, ANIMAL AND PLANT. By Gustav Seiffert. New York: F. Hubner & Co., 1944.

TROPICAL NURSING. By A. L. Gregg, M.D. New York: Philosophical Library, 1944.

TECHNIQUE IN TRAUMA. By Fraser B. Gurd, M.D., C.M., and F. Douglas Ackman, M.D., C.M. Philadelphia: J. B. Lippincott Co., 1944.

THE DENTAL TREATMENT OF MAXILLO-FACIAL INJURIES. By W. Kelsey Fry, M.C., R.C.S. (Eng.), P. Rae Shepherd, L.D.S., R.C.S. (Eng.), Alan C. McLeod, D.D.S., R.C.S. (Eng.), and Gilbert J. Parfitt, M.R.C.S., R.C.S. (Eng.). Philadelphia: J. B. Lippincott Co., 1944.

THE TREATMENT OF PEPTIC ULCER. By George J. Heuer, M.D. Philadelphia: J. B. Lippincott Co., 1944.

INFECTIONS OF THE PERITONEUM. By Bernhard Steinberg, M.D. New York: Paul B. Hoeber, Inc., 1944.

PRINCIPLES AND PRACTICES OF INHALATION THERAPY. By Alvan L. Barach, M.D. Philadelphia: J. B. Lippincott Co., 1944.

FERTILITY IN MEN. By Robert S. Hotchkiss, M.D. Philadelphia: J. B. Lippincott Co., 1944.

FERTILITY IN WOMEN. By Samuel L. Siegler, M.D. Philadelphia: J. B. Lippincott Co., 1944.

CATARACT AND ANOMALIES OF THE LENS. By John G. Bellows, M.D., Ph.D. St. Louis: C. V. Mosby Co., 1944.

HYPERTENSION AND HYPERTENSIVE DISEASE. By William Goldring, M.D., and Herbert Chosis, M.D. New York: The Commonwealth Fund, 1944.

INTRACRANIAL ARTERIAL ANEURYSMS. By Walter E. Dandy, M.D. Ithaca: Comstock Publishing Co., 1944.

BOOK REVIEW

INTRACRANIAL ARTERIAL ANEURYSMS. By Walter E. Dandy, Adjunct Professor of Surgery in The Johns Hopkins University. Pp. 147. Ithaca: Comstock Publishing Company, Inc., Cornell University, (1944).

This study is based on 108 cases of intracranial aneurysms. Of these, 44 were postmortem findings over a period of 50 years. The 64 cases disclosed at operation cover a period of 20 years. However, it is only a little over six years since the first planned operation for an aneurysm was carried out by the author. Since that time 36 aneurysms have been exposed at operation, all but three having been correctly diagnosed preoperatively. In 30 cases an attempt at surgical treatment was made, with resulting cures in 70 per cent.

Based on his experience the author found that the most favorable site for surgical treatment was the intracranial portion of the carotid prior to its branching.

A chapter on the development of the circle of Willis, by Dorcas Hager Padget, helps not only in the understanding of the site of origin of some of the aneurysms but sheds light on the possibility of untoward results following ligations. Because of frequent anomalies the remaining patent branches may be inadequate.

Informative tables of cases grouped on the basis of the vessel involved, an extensive bibliography and excellent illustrations round out this presentation of the author's experiences in a seldom trod path in neurologic surgery.

IRA COHEN, M.D.

STATEMENT OF THE OWNERSHIP, MANAGEMENT, CIRCULATION, ETC., REQUIRED BY THE ACTS OF CONGRESS OF AUGUST 24, 1912, AND MARCH 3, 1933 Of ANNALS OF SURGERY, published monthly at Philadelphia, Pa., as of December 1, 1944.

State of Pennsylvania } ss.
County of Philadelphia }

Before me, a Notary Public in and for the State and county aforesaid, personally appeared Ellis W. Bacon, who, having been duly sworn according to law, deposes and says that he is the Treasurer of the ANNALS OF SURGERY and that the following is, to the best of his knowledge and belief, a true statement of the ownership, management (and if a daily paper, the circulation), etc., of the aforesaid publication for the date shown in the above caption, required by the Act of August 24, 1912, as amended by the Act of March 3, 1933, embodied in section 537, Postal Laws and Regulations, printed on the reverse of this form, to wit:

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[Signed] ELLIS W. BACON.

Affirmed to and subscribed before me this 18th day of October, 1944.

[Seal] LILLIAN I. LIVINGSTON.

(My commission expires February 9, 1947.)

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